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(54) Title: **SIMULATION, MODELING AND SCHEDULING OF BATCH PROCESS MANUFACTURING FACILITIES USING PROCESS TIME LINES**

Unit Operations List

Microbial Fermentation Process

Unit No.	Code	Unit Operation Type	Cycle per				Process				Recovery			
			Unit Start	Unit End	Offset (hrs)	Unit Start	Unit End	Offset (hrs)	Unit Start	Unit End	Unit Start	Unit End	Offset (hrs)	Unit Start
1	1	Inoculum Prep	1	3	0	1	3	0	1	3	0	3	0	0
2	2	Batch Growth	1	3	0	1	3	0	1	3	0	3	0	0
3	3	Cold Fermentation	1	3	0	1	3	0	1	3	0	3	0	0
4	4	Production Fermentation	1	3	0	1	3	0	1	3	0	3	0	0
5	5	Heat Exchange	1	3	0	1	3	0	1	3	0	3	0	0
6	6	Heat Exchange	1	3	0	1	3	0	1	3	0	3	0	0
7	7	Heat Exchange	1	3	0	1	3	0	1	3	0	3	0	0
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10	10	Heat Exchange	1	3	0	1	3	0	1	3	0	3	0	0
11	11	Heat Exchange	1	3	0	1	3	0	1	3	0	3	0	0
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97	97	Heat Exchange	1	3	0	1	3	0	1	3	0	3	0	0
98	98	Heat Exchange	1	3	0	1	3	0	1	3	0	3	0	0
99	99	Heat Exchange	1	3	0	1	3	0	1	3	0	3	0	0
100	100	Heat Exchange	1	3	0	1	3	0	1	3	0	3	0	0

(57) Abstract: A system and method for simulating and modeling of biopharmaceutical batch process manufacturing facilities and a system and method for simulating, modeling and scheduling of related equipment preparation procedures. The method includes the step of selecting a sequence of unit operations (302) wherein each of the sequence of unit operations has an identifier code (304). Next, a set of scheduling cycles is selected for each of the sequence of unit operations. A block flow diagram is then generated using the sequence of unit operations and the operational parameters. The method further includes generating a process time line using the operational parameters, the block flow diagram, and the set of scheduling cycles for each of the sequence of unit operations.

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**SIMULATION, MODELING AND SCHEDULING OF BATCH PROCESS
MANUFACTURING FACILITIES USING PROCESS TIME LINES**

Background of the Invention

Field of the Invention

5 The present invention relates generally to the design of large scale batch manufacturing facilities, and specifically to the design of biopharmaceutical drug manufacturing processes and preparation and cleaning of soiled process components in the biopharmaceutical production process.

Related Art

10 Biopharmaceutical plants produce biopharmaceutical products through biological methods. Typical biopharmaceutical synthesis methods are mammalian cell culture, microbial fermentation and insect cell culture. Occasionally biopharmaceutical products are produced from natural animal or plant sources or by a synthetic technique called solid phase synthesis. Mammalian cell culture, microbial fermentation and insect cell culture involve the growth of living cells and the extraction
15 of biopharmaceutical products from the cells or the medium surrounding the cells. Solid phase synthesis and crude tissue extraction are processes by which biopharmaceuticals are synthesized from chemicals or extracted from natural plant or animal tissues, respectively.

 The process for producing biopharmaceuticals is complex. In addition to basic synthesis, additional processing steps of separation, purification, conditioning and formulation are required
20 to produce the end product biopharmaceutical. Each of these processing steps includes additional unit operations. For example, the step of purification may include the step of Product Adsorption Chromatography, which may further include the unit operations of High Pressure Liquid Chromatography (HPLC), Medium Pressure Liquid Chromatography (MPLC), Low Pressure Liquid Chromatography (LPLC), etc. The production of biopharmaceuticals is complex because
25 of the number, complexity and combinations of synthesis methods and processing steps possible. Consequently, the design of a biopharmaceutical plant is expensive.

Tens of millions of dollars can be misspent during the design and construction phases of biopharmaceutical plants due to inadequacies in the design process. Errors and inefficiencies are introduced in the initial design of the biopharmaceutical production process because no effective tools for modeling and simulating a biopharmaceutical production process exists. The
5 inadequacies in the initial process design carry through to all phases of the biopharmaceutical plant design and construction. Errors in the basic production process design propagate through all of the design and construction phases, resulting in increased cost due to change orders late in the facility development project. For example, detailed piping and instrumentation diagrams (P&IS) normally cost thousands of dollars per diagram. Problems in the biopharmaceutical production
10 process design frequently necessitate the re-working of these detailed P&IS. This adds substantially to the overall cost of design and construction of a biopharmaceutical plant.

There are generally three phases of biopharmaceutical plants which coincide with the different levels of drug approval by the FDA. A Clinical Phase I/II biopharmaceutical plant produces enough biopharmaceutical product to support both phase I and phase II clinical testing
15 of the product which may involve up to a few hundred patients. A Clinical Phase III biopharmaceutical plant produces enough biopharmaceutical product to support two to three-thousand patients during phase III clinical testing. A Clinical Phase III plant will also produce enough of the biopharmaceutical drug to support an initial commercial offering upon the licensing of the drug by the FDA for commercial sale. The successive phases represent successively larger
20 biopharmaceutical facilities to support full scale commercial production after product licensing. Often the production process design is repeated for each phase, resulting in increased costs to each phase of plant development.

The design, architecture and engineering of biopharmaceutical plants is a several hundred million dollars a year industry because of the complex nature of biopharmaceutical production.
25 Design of biopharmaceutical plants occurs in discrete phases. The first phase is the conceptual design phase. The first step in the conceptual design phase is identifying the high-level steps of the process that will produce the desired biopharmaceutical. Examples of high-level steps are synthesis, separation, purification and conditioning. After the high-level process steps have been identified, the unit operations associated with each of the high-level steps are identified. Unit
30 operations are discrete process steps that make up the high-level process steps. In a microbial

fermentation process, for example, the high-level step of synthesis may include the unit operations of inoculum preparation, flask growth, seed fermentation and production fermentation.

The unit operation level production process is typically designed by hand and is prone to errors and inefficiencies. Often, in the conceptual design phase, the specifications for the final production process are not complete. Therefore some of the equipment design parameters, unit operation yields and actual production rates for the various unit operations must be estimated. These factors introduce errors into the initial design base of the production process. Additionally, since the production process is designed by hand, attempting to optimize the process for efficiency and production of biopharmaceutical products is impractically time consuming.

Scale calculations for each of the unit operations are performed to determine the size and capacity of the equipment necessary to produce the desired amount of product per batch. Included in the scale calculations is the number of batches per year needed to produce the required amount of biopharmaceutical product. A batch is a single run of the biopharmaceutical process that produces the product. Increasing the size and capacity of the equipment increases the amount of product produced per batch. The batch cycle time is the amount of time required to produce one batch of product. The amount of product produced in a given amount of time, therefore, is dependent upon the amount produced per batch, and the batch cycle time. The scale calculations are usually executed by hand to determine the size and capacity of the equipment that will be required in each of the unit operations. Since the scale calculations are developed from the original conceptual design parameters, they are also subject to the same errors inherent in the initial conceptual design base.

Typically a process flow diagram is generated after the scale calculations for the unit operations have been performed. The process flow diagram graphically illustrates the process equipment such as tanks and pumps necessary to accommodate the process for a given batch scale.

The process flow diagram illustrates the different streams of product and materials through the different unit operations. Generally associated with the process flow diagram is a material balance table which shows the quantities of materials consumed and produced in each step of the biopharmaceutical production process. The material balance table typically includes rate information of consumption of raw materials and production of product. The process flow diagram and material balance table provides much of the information necessary to develop a

preliminary equipment list. The preliminary equipment list shows the equipment necessary to carry out all of the unit operations in the manufacturing procedure. Since the process flow diagram, material balance table and preliminary equipment list are determined from the original conceptual design parameters, they are subject to the same errors inherent in the initial conceptual design base.

A preliminary facility layout for the plant is developed from the process flow diagram, material balance table and preliminary equipment list. The preliminary facility layout usually begins with a bubble or block diagram of the plant that illustrates the adjacencies of rooms housing different high-level steps, as well as a space program which dimensions out the space and square footage of the building. From this information a preliminary equipment layout for the plant is prepared. The preliminary equipment layout attempts to show all the rooms in the plant, including corridors, staircases, etc. Mechanical, electrical and plumbing engineers estimate the mechanical, electrical and plumbing needs, respectively, of the facility based on the facility design layout and the utility requirements of the manufacturing equipment. Since the preliminary facility layout is developed from the original conceptual design parameters, they are subject to the same errors inherent in the initial conceptual design base.

Typically the next phase of biopharmaceutical plant design is preliminary piping and instrumentation diagram (P&ID) design. Preliminary P&IS are based on the process flow diagram from the conceptual design phase. Often the calculations on the process design are re-run and incorporated into the preliminary P&ID. The preliminary P&IS incorporate the information from the material balance table with the preliminary equipment list to show the basic piping and instrumentation required to run the manufacturing process.

Detailed design is the next phase of biopharmaceutical plant design. Plans and specifications which allow vendors and contractors to bid on portions of the biopharmaceutical plant are developed during the detailed design. Detailed P&IS are developed which schematically represent every detail of the process systems for the biopharmaceutical plant. The detailed P&IS include for example, the size and components of process piping, mechanical, electrical and plumbing systems; all tanks, instrumentation, controls and hardware. A bill of materials and detailed specification sheets on all of the equipment and systems are developed from the P&IS. Detailed facility architecture diagrams are developed that coincide with the detailed P&IS and

equipment specifications. The detailed P&IS and facility construction diagrams allow builders and engineering companies to bid on the biopharmaceutical plant project. Since the preliminary and detailed P&IS are developed from the original conceptual design parameters, they are subject to the same errors inherent in the initial conceptual design base. Reworking the preliminary and
5 detailed P&IS due to errors in the conceptual design phase can cost thousands of dollars per diagram.

The inability to accurately model and simulate the biopharmaceutical production process drives inaccurate initial design. Often, these inaccuracies result in changes to the design and construction diagrams at the plant construction site, or repair and reconstruction of the plant
10 during the construction phase resulting in millions of dollars in additional cost.

Once the biopharmaceutical production process has been determined, scheduling preparation of solutions for use in the biopharmaceutical production process drives the costs of the biopharmaceutical facility. Equipment, utility and cleaning equipment usage is primarily a function by the preparation and use of solutions in the biopharmaceutical production process.

15 After the biopharmaceutical production process and solution preparation process have been designed, the equipment preparation procedures for the cleaning of equipment soiled by the biopharmaceutical production process and solution preparation procedure must be determined. The protocols for cleaning soiled equipment are determined through experimentation and testing. Once the protocols and procedures for cleaning the soiled equipment have been determined,
20 however, it is difficult to determine the needed cleaning equipment capacity and the equipment cleaning procedure schedules necessary to clean the soiled process equipment. Often, designers of biopharmaceutical facilities design extra equipment preparation capacity into the biopharmaceutical facility in order to ensure a steady supply of clean, sterile equipment.

Current methods for the design equipment preparation procedures typically fall short of
25 accurately defining the relatively complex procedures that are executed in an equipment prep area. As a result the equipment and work areas associated with equipment prep are usually inefficiently designed. Cleaning and sterilizing (preparation) equipment associated with equipment preparation activities are capital and utility intensive, and inefficient designs result in increased costs of construction and operation of the biopharmaceutical facility.

What is needed, therefore, is a system and method for accurately simulating, modeling and scheduling biopharmaceutical production process and more specifically a system and method for accurately simulating, modeling and scheduling equipment preparation procedures in the biopharmaceutical production process.

- 5 A method and system for simulating, modeling and scheduling equipment preparation procedure in the biopharmaceutical production process would allow designers to reduce the number of errors introduced into plant design at the earliest stages. Such a system and method would also allow an engineer to validate the production process design and maximize the efficiency of the plant by finding optimum equipment configurations. Such a system and method
- 10 would allow the generation of detailed specifications for the preparation equipment and equipment preparation scheduling that would smooth the transition throughout all of the design phases and fix the cost of design and construction of a biopharmaceutical facility. The present invention can also be used for determining the cost of goods for a product.

Summary of the Invention

- 15 The present invention also satisfies the above-stated needs by providing a method and system for simulating and modeling of batch process manufacturing facilities using process time lines. The method includes the steps of identifying a production process sequence, the production process sequence including a plurality of subprocesses. At least one of the plurality of subprocesses includes a plurality of batch cycles, each of which includes a plurality of unit operations. Each of the unit
- 20 operations are identified by unit operation identifiers. Next, the system and method retrieves the process parameter information from a master list for each of the unit operation identifiers in the process sequence. The process parameter information includes information on discrete tasks associated with each unit operation. After the steps of identifying and retrieving, the system and method generates a process schedule that identifies initiation and completion times for each of the
- 25 discrete tasks in the process sequence. Next, a process time line using the operational parameters, the block flow diagram, the set of scheduling cycles for each of the sequence of unit operations is generated. The process time line is used as a tool for batch processing and facility design.

The present invention satisfies the above-stated needs by also providing a method and system for simulating, modeling and scheduling equipment preparation in the biopharmaceutical production process while optimizing the use of process vessels. The system and method includes the steps of identifying soiled process components and their associated equipment preparation procedures. After the soiled process components are identified, a master list of soiled process components and their associated equipment preparation procedure is generated. After the soiled process components and the equipment preparation procedures are identified, the equipment preparation procedures are scheduled out based on preparation equipment protocols to generate a equipment preparation load summary table. Next, the size and capacity of the preparation equipment is determined based on the information in the load summary table. After the size and capacity of the preparation equipment is determined, an equipment preparation time line is generated.

Brief Description of the Figures

The features and advantages of the present invention will become more apparent from the detailed description set forth below when taken in conjunction with the drawings in which like reference numbers indicate identical or functionally similar elements. Additionally, the left-most digit of a reference number identifies the drawing in which the reference number first appears.

FIG. 1 illustrates a flow diagram of the process to generate a block flow diagram and a process time line according to the present invention.

FIG. 2 illustrates a flow diagram of the process for determining the necessary reactor volume according to the present invention.

FIG. 3 illustrates a unit operation list for a microbial fermentation process.

FIG. 4 illustrates a unit operation list for a mammalian cell culture process.

FIG. 5 illustrates a flow diagram for cross-referencing a unit operation list with a process parameters table according to the present invention.

FIG. 6 illustrates an exemplary process parameters table.

FIG. 7 illustrates the process for generating a block flow diagram according to the present invention.

FIG. 8 illustrates an exemplary block flow diagram according to the present invention.

FIG. 9 illustrates a block flow diagram for the process of generating a process time line according to the present invention.

FIGS. 10-11 illustrate a high-level process time line according to the present invention.

5 FIGS. 12A-12H illustrate a detailed process time line according to the present invention.

FIG. 13 is a block flow diagram illustrating an overview of the process for scheduling and simulating solution preparation in a biopharmaceutical production process.

FIG. 14 is a block flow diagram illustrating the step of determining the solution preparation time associated with each solution preparation vessel.

10 FIG. 15 illustrates an exemplary list of solution preparation parameters.

FIG. 16 is a block flow diagram illustrating the step of assigning the solutions required by the biopharmaceutical production process to particular solution preparation vessels.

FIG. 17 illustrates an exemplary list of solution preparation procedure parameters.

FIG. 18 illustrates an exemplary preparation vessel to solution assignment list.

15 FIG. 19 illustrates an exemplary computer according to an embodiment of the present invention.

FIG. 20 is a block flow diagram illustrating the step of determining the calculated preparation start date and next solution preparation date for each solution.

FIG. 21 illustrates an exemplary master quality control protocol table.

20 FIG. 22 is a block flow diagram illustrating the step of generating a solution preparation equipment quality control time line.

FIG. 23 is a block flow diagram illustrating the step of generating a preparation equipment quality control time line.

25 FIG. 24 is a block flow diagram illustrating the step of determining the earliest solution preparation start date for each solution preparation vessel.

FIG. 25 is a block flow diagram illustrating the step of determining the latest solution preparation start date for each solution preparation vessel.

FIG. 26 is a block flow diagram illustrating the step of calculating solution preparation vessel utilization time.

FIG. 27 is a block flow diagram illustrating the step of calculating the cumulative solution preparation time for each solution preparation vessel.

FIG. 28 is a block flow diagram illustrating the step of determining the percentage utilization of each solution preparation vessel.

5 FIG. 29 is a block flow diagram illustrating the step of generating an initial solution prep shift schedule.

FIG. 30 is a block flow diagram illustrating the step of back scheduling solution preparation in the initial solution prep shift schedule.

FIG. 31 illustrates an exemplary initial solution preparation shift schedule.

10 FIG. 32 is a block flow diagram illustrating the process for generating a solution preparation schedule.

FIG. 33 is a block flow diagram illustrating an overview of the process for scheduling and simulating solution preparation in a biopharmaceutical production process.

15 FIG. 34 is a block flow diagram illustrating the step of generating the preparation equipment protocol table.

FIG. 35 is a block flow diagram illustrating the step of generating the equipment preparation procedure table.

FIGS. 36A-36H illustrate exemplary preparation equipment protocol tables.

FIGS. 37A-37B illustrate an exemplary equipment preparation procedure table.

20 FIG. 38 is a block flow diagram illustrating the step of generating the equipment dimension table.

FIG. 39 illustrates an exemplary equipment dimension table.

FIG. 40 is a block flow diagram illustrating the step of generating the master list of equipment requiring preparation.

25 FIG. 41 is a block flow diagram illustrating the step of generating the equipment preparation load table.

FIGS. 42A-42D illustrate an exemplary equipment preparation load table.

FIG. 43 is a block flow diagram illustrating the step of generating the equipment preparation load summary table.

FIG. 44 is a block flow diagram illustrating the step of determining the capacities of the preparation equipment.

FIGS. 45A-45I illustrate an exemplary process equipment quality control assay sample time line.

5 FIG. 46 is a block flow diagram illustrating the step of generating the equipment preparation time line.

FIG. 47 is a block flow diagram illustrating the step of generating the preparation equipment list with functional specification and costs.

10 FIG. 48 is a block flow diagram illustrating the step of generating the preparation equipment utility time line.

FIG. 49 is a block flow diagram illustrating the step of generating a process equipment maintenance table.

FIG. 50 is a block flow diagram illustrating the step of generating a process equipment maintenance time line.

15 FIG. 51 is a block flow diagram illustrating the step of generating a solution preparation equipment maintenance table.

FIG. 52 is a block flow diagram illustrating the step of generating a solution preparation equipment maintenance time line.

20 FIG. 53 is a block flow diagram illustrating the step of generating a preparation equipment maintenance table.

FIG. 54 is a block flow diagram illustrating the step of generating a preparation equipment maintenance time line.

FIG. 55 is a block flow diagram illustrating the step of generating a process equipment calibration table.

25 FIG. 56 is a block flow diagram illustrating the step of generating a process equipment calibration time line.

FIG. 57 is a block flow diagram illustrating the step of generating a solution preparation equipment calibration table.

30 FIG. 58 is a block flow diagram illustrating the step of generating a solution preparation equipment calibration time line.

FIG. 59 is a block flow diagram illustrating the step of generating a preparation equipment calibration table.

FIG. 60 is a block flow diagram illustrating the step of generating a preparation equipment calibration time line.

5 FIG. 61 is a block flow diagram illustrating the step of generating a master quality control protocol table.

FIG. 62 is a block flow diagram illustrating the step of generating a master quality control sample table.

10 FIG. 63 is a block flow diagram illustrating the step of generating a process equipment quality control time line.

FIGS. 64A-64AB illustrate an exemplary process equipment maintenance time line.

FIG. 65 not used.

FIG. 66 is a block flow diagram illustrating a divergent and convergent process flow schemes according to an embodiment of the present invention.

15 FIG. 71 is an exemplary Material Consumption Table.

FIGS. 67-70 and 72-81 are block flow diagrams that illustrate the simulation and modeling of solution formulations used in multiple points of a batch process facility according to an embodiment of the present invention.

20 FIG. 82 illustrates a refined unit operation list for a mammalian cell culture process according to an embodiment of the present invention.

FIG. 83 illustrates a refined unit operation list for a microbial fermentation process according to an embodiment of the present invention.

FIG. 84A-F illustrate a refined process time line for a mammalian cell culture process according an embodiment of the present invention.

25 FIG. 85 is a flow chart that illustrates the method for determining the impact of design cycle offsets on the current critical path start time for a respective unit operation cycle.

FIG. 86 is a flow chart that illustrates the test for a new batch cycle according to an embodiment of the present invention.

30 FIG. 87 is a flow chart that illustrates the test for a new unit operation cluster cycle according to an embodiment of the present invention.

FIG. 88 is a flow chart that illustrates the test for a new unit operation cycle according to an embodiment of the present invention.

FIGs. 89-95 is a flow chart that illustrates the determination of start/stop times for various cycles according to an embodiment of the present invention.

5 FIG. 96A-96G is a detailed example of a process parameters table showing a list of unit operations and their associated parameters.

Detailed Description of the Preferred Embodiments

1.0 Biopharmaceutical Batch Process Simulator

FIG. 1 illustrates a high-level flow diagram of the preferred embodiment. The process
10 begins by determining the necessary reactor vessel capacity at step 102. The reactor vessel is the container in which the crude product is first synthesized. For example, in mammalian cell culture processes, the reactor vessel houses the mammalian cells suspended in growth media. Next, the unit operation sequence for production of the biopharmaceutical product is determined at step 104. The unit operation sequence is the series of unit operations that are required to produce the
15 biopharmaceutical product. Each unit operation is an individual step in the biopharmaceutical manufacturing process with an associated set of manufacturing equipment. The unit operation list is the list of unit operations that make up the unit operation sequence and their associated sequence information. The unit operation sequence information is the information that defines the scheduling cycles for each of the unit operations in the unit operation list. Scheduling cycles are
20 iterations (the default being one (1)) of unit operations in the unit operation sequence. Together, the unit operation list and the unit operation sequence information define the unit operation sequence. The desired biopharmaceutical product dictates the particular unit operations and their order in the biopharmaceutical production process. Some examples of unit operations are: inoculum preparation, initial seeding of the reactor vessel, solids harvest by centrifugation, high-
25 pressure homogenization, dilution, etc.

Scheduling cycles and cycle offset duration for each of the unit operations in the biopharmaceutical production process are determined at step 106. Scheduling cycles are iterations

of unit operations in the unit operation sequence, and occur in three levels. Additionally, each level of scheduling cycle has an associated offset duration that dictates the time period between the beginnings successive scheduling cycles.

"Unit Operation Cycles" (UC) or "Cycles per unit operation" is the first level of scheduling cycles. Cycles per unit operation are defined as the number of iterations a unit operation is repeated in a process by itself before proceeding to the next operation. For example, the harvest and feed unit operation in a mammalian cell culture process has multiple cycles per unit operation. Product-rich media is drawn from the reactor vessel and nutrient-rich media is fed into the reactor vessel multiple times during one harvest and feed unit operation. The multiple draws of product-rich reactor media are pooled for processing in the next unit operation.

The second level of scheduling cycles is "Unit Operation Cluster Cycles" (CC) or "cycles per batch." Cycles per batch are defined as the number of iterations a set of consecutive unit operations are repeated as a group before proceeding to the next unit operation after the set of consecutive unit operations. The set of consecutive unit operations repeated as a group are also referred to as a subprocess. For example, the set of unit operations including inoculum preparation, flask growth, seed fermentation, production fermentation, heat exchange, and continuous centrifugation/whole-cell harvest in a microbial fermentation process are often cycled together. Running through each of the six steps results in a single harvest from the microbial fermentation reactor vessel. Multiple harvests from a reactor vessel may be needed to achieve a batch of sufficient quantity. Each additional harvest is pooled with the previous harvest, resulting in a single batch of cell culture for the process.

The third level of scheduling cycles is "Batch Cycles" (BC) or "cycles per process." Cycles per process are defined as the number of iterations a batch cycle is repeated for a process that employs continuous or semi-continuous product synthesis. In such a case, a single biopharmaceutical production process may result in multiple batches of product. For example, in a mammalian cell-culture process a single cell culture is typically in continuous production for 60-90 days. During this period multiple harvests of crude product are collected and pooled on a batch basis to be processed into the end product biopharmaceutical. The pooling of multiple harvests into a batch of material will occur several times during the cell culture period resulting in multiple batch cycles per process.

In step 108, a process parameters table master list is referenced to obtain all operational parameters for each unit operation in the unit operation list. The process parameters table contains a list of all unit operations and operational parameters necessary to simulate a particular unit operation. Examples of operational parameters are the solutions involved in a particular unit operation, temperature, pressure, duration, agitation, scaling volume, etc. Additionally, the process parameters table supplies all of the individual tasks and task durations involved in a particular unit operation. For example, the unit operation of inoculum preparation includes the individual tasks of setup, pre-incubation, incubation, and cleanup. Examples of unit operations for biopharmaceutical manufacturing and their associated operational parameters are included in this application as FIG. 96A-96G.

A block flow diagram is generated at step 110 after unit operation list has obtained the operational parameters from the process parameters table at step 108. The block flow diagram illustrates each unit operation in the manufacturing process as a block with inputs for both incoming product and new material, as well as outputs for both processed product and waste. The block flow diagram is a simple yet convenient tool for quantifying material flows through the process in a way that allows the sizing of many key pieces of equipment relative to a given process scale.

The information in each block of the block flow diagram is generated from the parameters and sizing ratios from the process parameters table in the unit operation list, and block flow diagram calculation sets. A calculation set is a set of algebraic equations. The parameters and calculation sets are used to calculate the quantities of material inputs, product and waste outputs required for that unit operation based on the quantity of product material being received from the previous unit operation. Likewise, a given block flow diagram block calculates the quantity of product to be transferred to the next unit operation block in the manufacturing procedure. These calculations take into account the unit operation scheduling cycles identified at step 106, as further explained below.

A process time line is generated at step 112 after the block flow diagram is generated at step 110. The process time line is a very useful feature of the present invention. The process time line is generated from the unit operation list, the tasks associated with each of the unit operations, the scheduling cycles for each of the unit operations in the process, the process

parameters from the master process parameters table and the volume of the material as calculated from the block flow diagram. The process time line is a relative time line in hours and minutes from the start date of the production process. The relative time is converted into days and hours to provide a time line for the beginning and ending times of each unit operation and its associated tasks for the entire biopharmaceutical drug production process.

The process time line is a very powerful tool for process design. The process time line can be used to accurately size pumps, filters and heat exchangers used in unit operations, by calculating the flow rate from the known transfer time and the volume of the material to be transferred, filtered or cooled. The process time line accurately predicts loads for labor, solution preparation, equipment cleaning, reagent, process utilities, preventative maintenance, quality control testing, etc.

FIG. 2 further illustrates step 102 of determining the necessary reactor vessel capacity. The amount of biopharmaceutical product to be produced in a given amount of time is determined in step 202. Normally, the amount of biopharmaceutical product required is expressed in terms of mass produced per year. The number of reactor vessel runs for a particular biopharmaceutical product per year is determined at step 204. Factors considered when determining the number of reactor vessel cycles for a particular biopharmaceutical product are, for example, the number of biopharmaceutical products produced in the reactor vessel (i.e., the reactor vessel is shared to produce different products), the reaction time for each cycle of the reactor vessel and the percentage of up-time for the reactor vessel over the year.

The yield of each batch or reactor cycle is calculated at step 206. The yield from each batch or a reactor cycle is process-dependent and is usually expressed in grams of crude product per liter of broth. Given the required amount of biopharmaceutical product per year from step 202, the number of reactor cycles available to produce the required biopharmaceutical product from step 204, and the yield of each reactor cycle from step 206, the necessary reactor volume to produce the required amount of biopharmaceutical product is calculated at step 208.

FIG. 3 illustrates a unit operation list for an exemplary microbial fermentation biopharmaceutical production process. The far left-hand column, column 302, lists the unit operation sequence numbers for each of the unit operations in the process. The exemplary microbial fermentation unit operation list includes 23 unit operations. The unit operation

sequence number defines the order in which the unit operations occur. For example, unit operation sequence number 1, inoculum preparation, occurs first, before unit operation sequence number 2, flask growth. Column 304 shows the unit operation identifier codes associated with each of the unit operations in the unit operation list (see step 108). The unit operation identifier codes are used to bring operational parameters from the process parameters table into the unit operation list. For example, heat exchange, unit operation list numbers 5, 8 and 10, has a unit operation identifier code 51.

As described above with reference to FIG. 1, after the unit operation sequence for a particular biopharmaceutical production process has been determined at step 104, the scheduling cycles associated with each unit operation is determined at step 106. Columns 306, 310 and 318 list the number of scheduling cycles for the microbial fermentation process of FIG. 3. Scheduling cycles are iterations of unit operations in the unit operation sequence, and occur in three levels. Additionally, each level of scheduling cycle has an associated offset duration that dictates the time period between the beginnings of successive scheduling cycles, shown in columns 308, 316 and 324.

Column 306 lists the number of cycles per unit operation for each of the unit operations in the microbial fermentation unit operation sequence. In the exemplary microbial fermentation unit operation sequence, each of the unit operations has only one cycle per unit operation. Again, cycles per unit operation define the number of iterations a unit operation is repeated in a process by itself before proceeding to the next unit operation.

Column 308 lists the cycle offset duration in hours for the cycles per unit operation. Since each of the unit operations in the microbial fermentation example of FIG. 3 has only one cycle per unit operation, there is no cycle offset duration for any of the unit operations. Cycle offset duration defines the time period between the beginnings of successive scheduling cycles.

Column 310 lists the cycles per batch for each of the unit operations in the microbial fermentation unit operation sequence. Unit operation sequence numbers 1-6 are defined as having three cycles per batch. Cycles per batch defines the number of iterations a set of consecutive unit operations are repeated as a group before proceeding to the next unit operation. In FIG. 3, for example, the set of unit operations 1-6, as defined in unit operation start column 312 and unit operation end column 314, cycle together as a group (e.g., the sequence of unit operations for the

exemplary microbial fermentation process is 1, 2, 3, 4, 5, 6, 1, 2, 3, 4, 5, 6, 1, 2, 3, 4, 5, 6 and 7). Unit operations 1-6 cycle together as a group three times before the process continues to unit operation 7, as defined in column 310.

After unit operation sequence numbers 1-6 have cycled consecutively three times, the microbial fermentation production process continues at unit operation sequence number 7, resuspension of cell paste. After unit operation sequence number 7, the process continues with three cycles per batch of unit operation sequence numbers 8-10. The unit operations of heat exchange, cell disruption and heat exchange are cycled consecutively three times, as defined in columns 310, 312 and 314. After unit operation sequence numbers 8-10 have cycled three times, the microbial fermentation production process continues at resuspension/surfactant, unit operation sequence number 11.

Unit operation sequence numbers 11 and 12 cycle together two times, as defined by columns 310, 312 and 314. After unit operation sequence numbers 11 and 12 have been cycled two times, the microbial fermentation production process continues without cycling from unit operation sequence number 13 through unit operation sequence number 23 to conclude the microbial fermentation production process.

Columns 326-332 of FIG. 3 represent the step wise recover (SWR) and overall recovery (OAR) percentages of the product and total proteins. SWR is the recovery of protein for the individual unit operation for which it is listed. OAR is the recovery of protein for the overall process up to and including the unit operation for which it is listed. The product recovery columns represent the recovery of the desired product protein from the solution in the process. The protein recovery columns represent the recovery of contaminant proteins from the solution which result in higher purity of the product solution.

FIG. 4 illustrates a unit operation list for an exemplary mammalian cell culture production process. Column 402 lists unit operation sequence numbers 1-19. Unit operation sequence numbers 1-19 define the order in which the unit operations of the mammalian cell culture production process occur. The most notable differences between the microbial fermentation process of FIG. 3 and the mammalian cell culture process of FIG. 4 are the multiple cycles per unit operation of unit operation sequence number 8 and the multiple cycles per process of unit operation sequence numbers 8-18.

Unit operation sequence number 8 of FIG. 4 illustrates the concept of multiple cycles per unit operation. Unit operation sequence number 8 is the unit operation of harvesting product rich growth media from and feeding fresh growth media into the mammalian cell reactor vessel. In most mammalian cell culture processes, the product is secreted by the cells into the surrounding growth media in the reactor vessel. To harvest the product, some of the product rich growth media is harvested from the reactor vessel to be processed to remove the product, and an equal amount of fresh growth media is fed into the reactor vessel to sustain production in the reactor vessel. The process of harvesting and feeding the reactor vessel can continue for many weeks for a single biopharmaceutical production process. Unit operation sequence number 8 is repeated seven times, or 7 cycles per unit operation (e.g., the unit operation sequence is 7, 8, 8, 8, 8, 8, 8, 8, 9). Note that the offset duration for unit operation sequence number 8 is 24 hours. The offset duration defines the time period between the cycles per unit operation. In the example of FIG. 4, unit operation sequence number 8 is repeated 7 times (7 cycles per unit operation) and each cycle is separated from the next by 24 hours, or one day. This corresponds to unit operation sequence number 8 having a duration of one week, with a harvest/feed step occurring each day.

FIG. 4 also illustrates the feature of multiple cycles per process. Cycles per process is defined as the number of iterations a batch cycle is repeated in a given process that employs continuous or semi-continuous product synthesis. Each batch cycle results in a batch of product. A single biopharmaceutical production process, therefore, may result in multiple batches of product. In the mammalian cell culture process example of FIG. 4, unit operation sequence numbers 8-18 are repeated together as a group eight times (column 418). Each of these cycles of unit operation sequence numbers 8-18 produce one batch of product (columns 420-422). The offset between each cycle of unit operation sequence numbers 8-18 is 168 hours, or one week (column 424).

In the example of FIG. 4, unit operation sequence numbers 8-18 proceed as follows: the reactor vessel is harvested and fed once each day for seven days; the results of the harvest/feed operation are pooled in unit operation sequence number 9 at the end of the seven days; unit operations 9-18 are then executed to process the pooled harvested growth media from unit operation sequence number 8. Unit operation sequence numbers 8-18 are cycled sequentially once

each week to process an additional seven day batch of harvested growth media from unit operation sequence number 8. At the end of eight weeks, the mammalian cell culture process is completed.

FIG. 5 further illustrates step 108, cross referencing the unit operation sequence with the master process parameters table. The operational parameters in the process parameters table are those parameters necessary to simulate a particular unit operation. The parameters from the process parameters table define the key operational parameters and equipment sizing ratios for each unit operation in the unit operation sequence. The values for these parameters and ratios are variables which can be easily manipulated and ordered to model and evaluate alternative design scenarios for a given process scale. Examples of the process parameters associated with each unit operation are shown in FIG. 96A-96G. It should be noted, however, that the list of unit operations, parameters, values, and scaling ratios is not exhaustive. One of ordinary skill in the art could expand the process parameters table to encompass additional unit operations and production processes for other batch process industries such as chemical pharmaceutical, specialty chemical, food, beverage and cosmetics. Such expansion would allow the present invention to simulate and schedule additional batch production processes for other such batch processes.

FIG. 5 illustrates the files necessary to cross-reference the unit operation list with the process parameters table in step 108. Exemplary unit operation list 502 for the biopharmaceutical production process and process parameters table 504 are input into processing step 506. Step 506 cross-references the unit operation list and process parameters table based on unit operation identification code (see FIG. 3). The parameters are copied from the process parameters table 504 into the unit operation list 502 to generate unit operation list 508.

FIG. 6 further illustrates exemplary process parameters table, 504. The operational parameters in the process parameters table are those parameters necessary to simulate a particular unit operation. The unit operation identification codes of process parameters table 504 are used in the cross-reference step 506 to assign the parameters from the process parameters table 504 to the unit operation list 502. Examples of operational parameters are the solutions involved in a particular unit operation, temperature, pressure, duration, agitation, scaling volume, etc. Additionally, the process parameters table defines all of the individual tasks and task durations involved in each unit operation. It should be noted, however, one of ordinary skill in the art could expand the process parameters table to encompass additional unit operations and production

processes for other batch process industries such as chemical pharmaceutical, specialty chemical, food, beverage and cosmetics. Such expansion would allow the present invention to simulate and schedule additional batch production processes for other such batch processes.

FIG. 7 further illustrates step 110, generating a block flow diagram. A block flow diagram depicts each unit operation in the biopharmaceutical production process as a block with inputs for both incoming product and new material, as well as outputs for both processed product and waste. The material that flows through each of the unit operation blocks is quantified by calculation sets in each of the block flow diagram blocks. A unit operation block in a block flow diagram is a graphical representation of a unit operation. A calculation set is a set of algebraic equations describing a unit operation. Some examples of outputs of the calculation sets are: required process materials for that unit operation, equipment performance specifications and process data outputs to be used for the next unit operation. Some examples of inputs to the calculation sets are: product quantity (mass) or volume (liters) from a previous unit operation, other parameters and/or multipliers derived from the process parameters table, as well as the design cycles defined in the unit operation list.

Block flow diagram 708 is generated from unit operation list 508 and block flow diagram calculation set 704. Block flow diagram calculation set 704 is an exhaustive list of unit operation identifier codes and the calculation sets associated with each unit operation identifier. Unit operation list 508 and block flow diagram calculation set 704 are linked together based on unit operation identifier code.

Step 706 calculates the block flow diagram material flow requirements and basic equipment sizing requirements from unit operation list 508 which includes all of the associated operational parameters from the process parameters table, and the block flow diagram calculation set 704. Block flow diagram 708 allows the sizing of many key pieces of equipment relative to a given process scale. Since the material flow quantities into and out of each unit operation is determined at step 706, the capacity of many equipment items involved in each unit operation can be determined. The block flow diagram also manages important information in the unit operation list 502 such as the percent recovery, percent purity and purification factor of the product in each unit operation. This information helps identify the steps in the process that may need optimization.

The following is an example calculation set for a tangential flow micro-filtration (TFMF) system unit operation. Tangential flow micro-filtration is an important process technology in biopharmaceutical manufacturing. This technology significantly extends the life of the filtration media and reduces the replacement cost of expensive filters.

- 5 TFMF generically requires the same steps to prepare the membrane for each use as well as for storage after use. The design parameters for each unit operation such as TFMF have been developed around these generic design requirements.

Generic Parameters (Variables) from the Process Parameters Table

	Equipment Design Type	Plate & Frame
10	Membrane Porosity	0.2 micron
	Membrane Flux rate	125 Liters/square meter/hour
	Process Time	2 Hours
	Retentate/Filtrate Rate	20 to 1
	Flush volume	21.5 Liters/square meter
15	Prime volume	21.5 Liters/square meter
	Wash Volume	0.5 % of Process Volume
	Regenerate Volume	10.8 Liters/square meter
	Storage Volume	21.5 Liters/square meter
	% Recovery of Product	95%
20	% Recovery of Total Protein	80%
	Clean In Place (CIP)	Yes
	Steam In Place (CIP)	Yes

Input Values from Previous Unit Operation

	Product Volume	1,000 Liters
25	Product Quantity	1.5 Kg
	Total Protein Quantity	3.0 Kg

The calculation set for this unit operation first takes the incoming process volume and uses it as a basis of sizing the filtration membrane for the filtration system based on the above flux rate and required processing time.

$$1,000 \text{ Liters} / 125 \text{ L/SM/Hr} / 2 \text{ Hours} = 4.0 \text{ SM of 0.2 micron membrane}$$

- 5 After calculating the square meter (SM) of membrane required by this unit operation, the volumes of each of the support solutions can be calculated based on the above volume ratios.

	Flush Volume	$21.5 \text{ Liters/SM} \times 4.0 \text{ SM} = 86 \text{ Liters}$
	Prime Volume	$21.5 \text{ Liters/SM} \times 4.0 \text{ SM} = 86 \text{ Liters}$
	Wash Volume	$5 \% \text{ of } 1,000 \text{ Liters} = 50 \text{ Liters}$
10	Regenerate Volume	$21.5 \text{ Liters/SM} \times 4.0 \text{ SM} = 86 \text{ Liters}$
	Storage Volume	$10.8 \text{ Liters /SM} \times 4.0 \text{ SM} = 42 \text{ Liters}$

The flow rate of the filtrate is calculated from the volume to be filtered and the required process time.

$$1,000 \text{ Liters} / 2 \text{ Hours} = 8.3 \text{ Liters/minute}$$

- 15 The flow rate of the retentate is calculated based on the above retentate/filtrate ratio.

$$8.3 \text{ Liters/minute} \times 20 = 167 \text{ Liters/minute}$$

Based on the input of the process volume to this unit operation and the above parameters, the equipment size, the filtration apparatus, the retentate pump, the support linkage and associated systems can be designed.

- 20 In addition, the input values for the quantity of product and contaminant protein received from the previous unit operation together with the recovery factors listed in the parameters allow the calculation of the cumulative recovery of product through this step, as well the percent purity

of the product and the product purification factor for this step. This information is helpful for identifying steps in the manufacturing process which require optimization.

FIG. 8 illustrates an exemplary block flow diagram for the first five unit operations of the microbial fermentation process unit operation list of FIG. 3. Unit operations 1 through 5 are shown as blocks 802, 804, 806, 808 and 810. The input solutions to each of the steps are shown as arrows tagged with solution identifier information from the unit operation list 508. The process streams to which these solutions are added at each unit operation are also shown as arrows tagged with process stream identifier information. Working from the initial process stream characteristics (P-101) in unit operation 1, inoculum prep, the volumes of input materials (solutions) and subsequent process streams in each of the unit operations is determined using scale-up ratios which are included in the information from the unit operation list 508 for each respective unit operation. For example, the volume of solutions and process streams flowing into and out of each of unit operation blocks 802-810 in FIG. 8 is determined by the initial starting characteristics of the process stream P-101 and the volume of its associated input material S-101 in the first unit operation, block 802 and the scale up ratio in each of the successive unit operations, blocks 804-810. The solutions involved in each of unit operation blocks 802-810 are likewise part of the information for each respective unit operation in the unit operation list 508.

FIG. 9 further illustrates step 112, generating the process time line. The process time line is generated (steps 904-906) from unit operation list 508 and block flow diagram calculation set 704. Unit operation list 508 contains enough input information to generate a detailed process time line which includes the start and stop times for most of the tasks associated with each unit operation. The durations of some unit operation tasks are not scale dependent. The durations of other unit operation tasks are, however, scale dependent. In the latter case, as a process is scaled up, the amount of time required to complete a unit operation task increases. In such cases, where duration of a unit operation task is scale dependent, block flow diagram calculation set 704 is required to calculate the quantity of material handled by the unit operation task. After the quantity of material handled by a unit operation task is determined, its duration can be determined. Examples of scale dependent task durations are the time required to pump solutions from one storage tank to another, the amount of time required to heat or cool solutions in a heat exchanger, the amount of time required to filter product or contaminants from solution.

FIG. 10 is an example of a high-level process time line for a microbial fermentation process. The unit operation sequence of the process time line of FIG. 10 corresponds to the unit operation list of FIG. 3. The high-level process time line shown in FIG. 10 illustrates two process cycles of the microbial fermentation unit operation sequence, labeled "First Process Cycle" and "Second Process Cycle." A process cycle is a complete run of the biopharmaceutical production process, as defined by the unit operation sequence for the process.

The first two columns of the process time line of FIG. 10 identify the unit operation sequence number and unit operation description of the unit operation being performed, respectively. The first three sets of unit operations correspond to the three cycles per batch of unit operation sequence numbers 1-6 of FIG. 3. Three cycles of unit operations 1-6 are performed and the results are pooled into unit operation 7, pool harvests. The two columns to the right of the duration column identify the week and day that the particular unit operation is occurring in the first process cycle.

The day and the week each unit operation is performed is calculated from the start time of the process, as well as the cumulative duration of each of the previous unit operations. In the example of FIG. 10, Sunday is defined as the first day of the week. In the example of FIG. 10, the process sequence begins at unit operation 1, inoculum prep, on Friday of the first week. After unit operation 1 has completed (24 hours later, since unit operation 1 has a 24 hour duration) unit operation 2 is performed on Saturday. The begin and end times for each successive unit operation are calculated from the duration of the unit operation and end time of the previous unit operation. Note that FIG. 10 is calculated to the day and week only for the purposes of explanation. Usually the process time line is determined for each of the tasks associated with a unit operation to the minute.

As illustrated in FIG. 10, unit operation 7 occurs on Monday of the third week in the first process cycle. The third column from the left is the duration of each of the unit operations. After the three cycles of unit operations 1 through 6 have been pooled in unit operation 7, the process continues at unit operations 8 through 10, heat exchange, cell disruption and heat exchange. Each of unit operations 8 through 10 are cycled three times and the associated scheduling information is contained in column to the right of the unit operation duration. Since each cycle of unit

operations 8 through 10 have a duration of .5 hours, as shown in column 3, each cycle occurs on Monday of the third week in the process.

FIG. 11 illustrates the final unit operations of the process time line for the microbial fermentation process. After 3 cycles of unit operations 8 through 10 have been completed, unit operation sequence numbers 11 and 12 cycle together two times on Monday, week 3 of the first process cycle. After unit operation sequence numbers 11 and 12 have been cycled twice, the microbial fermentation production process continues without cycling from unit operation sequence number 13 through unit operation sequence number 22 to conclude the microbial fermentation production process. The durations and associated start times are listed for each of the unit operations 13-22.

FIGS. 12A-12H illustrate the preferred embodiment of a detailed process time line. The unit operation sequence of the process time line of FIGS. 12A-12H correspond to the unit operation list of FIG. 3. The process time line of FIGS. 12A-12H illustrates a single process cycle of the microbial fermentation unit operation sequence. The individual tasks associated with each unit operation are included after the unit operation. For example, in FIG. 12A, unit operation 1A, inoculum prep, consists of the individual tasks of set up, pre-incubation, incubation, and clean up. Columns 11-14 show the start date and time and finish date and time for each of the tasks in each unit operation. Since setup and clean up are not part of the critical path of the process, they do not directly affect the start and end times of following unit operations. The start and finish date and times for the set up and clean up operations of each of the unit operations are valuable because they ensure that the equipment will be available for each unit operation if the process time line is followed.

The process time line of FIGS. 12A-12H includes examples of unit operation task duration calculations. Row 20, column 15 of FIG. 12A, which corresponds to the harvest task of unit operation 3A, seed fermentation, is an example of a duration calculation. As stated above, the duration of some unit operations is process scale dependent (i.e., the duration is dependent upon the volume processed). The harvest task in the seed fermentation unit operation is an example of a task whose duration is process scale dependent. In column 15, the calculations column, information listed for the harvest task is 50 liters, 1.7 liters/minute (LPM), and 0.5 hours. Fifty liters represents the volume of material that is harvested during a harvest task. 1.7 liters/minute

represents the rate at which the solution is harvested. Given the volume to be harvested and the flow rate of the harvest, the duration of the harvest task is calculated to be 0.5 hours. Each task in a unit operation that is volume dependent has its duration calculated in order to generate the process time line of FIGS 12A-12H.

5 The process time line of FIGS. 12A-12H can be resolved to minutes and seconds, if necessary. The accuracy of the process time line allows the precise planning and scheduling of many aspects of the batch manufacturing process. The process time line scheduling information can be used to schedule manufacturing resources such as labor, reagents, reusables, disposables, etc., required directly by the manufacturing process. Pre-process support activities such as
10 solution preparation, and equipment prep and sterilization, required to support the core process, including the labor, reagents, etc. can be scheduled, cost forecasted and provided for. Post-process support activities such as product formulation, aseptic fill, freeze drying, vial capping, vial labeling and packaging required to ship the purified product in a form ready for use may be added to the process time line and managed. Based on the process time line, labor, reagents, etc.,
15 required to support these post-process support functions can be acquired and managed. One of the most important aspects of the present invention is the determination of process utility loads such as USP Purified Water, Water For Injection, Pure Steam, etc., for all of the manufacturing equipment. The process time line can be used to determine the peak utility loading, and utility requirements for the facility. Building utility loads such as building steam, heating, ventilation,
20 air conditioning, plumbing, etc., for all manufacturing equipment, process areas and facility equipment can be determined based on the process time line and the equipment associated with each of the unit operations. The process time line can be used to measure the time that the equipment has been in service to schedule preventative maintenance of all plant equipment, Quality Assurance activities including instrument calibration, automated batch documentation, etc.
25 and Quality Control activities including process system maintenance, raw material testing, in process testing and final product testing, etc.

In an alternative embodiment of the present invention, a refinement can be made to the generation of a process time line (PTL), as shown in FIG. 9 (step 112 of FIG. 1), based on the three levels of scheduling cycles--"Unit Operation Cycles," "Unit Operation Cluster Cycles," and "Batch
30 Cycles"--discussed above.

The refinement (i.e., new mechanism) focuses on how to apply the offsets associated with each design cycle to the PTL. In cases where the offset for any of the levels of scheduling cycles is equal to zero, as soon as the cycle is completed it immediately begins the next cycle at that same cycle level, assuming another cycle has been specified. Otherwise, the scheduling mechanism passes
 5 to the next unit operation specified and its respective set of cycle conditions. This new mechanism clarifies the impact an offset of greater than zero for any of the scheduling cycle levels has on the PTL.

To implement this new mechanism, a unit operation tagging convention based on a four-field delimited string is used to identify each cycle iteration of a unit operation module in a PTL (PTLM)
 10 by its respective cycle level and cycle count. A PTLM is a section of the PTL having a set of tasks with respective scheduling calculations that are associated with a given unit operation. The above delimited fields are defined as follows:

DELIMITED FIELD	VALUE
Field 1	Unit Operation Sequence Number
Field 2	Batch Cycle Iteration
Field 3	Cluster Cycle Iteration
Field 4	Unit Operation Cycle

Together, the four-fields of the delimited string makes up a Delimited String Code (DSC) (e.g.,
 20 "3.2.1.1") that provides a unique identifier for each PTLM in the PTL. The DSCs are based upon the above-described sequence and design cycle information for each design cycle iteration for each unit operation in the PTL.

As discussed above, a PTL consists of unit operations decomposed into unit operation tasks that are required to complete a unit operation procedure. These tasks can be divided in to three basic
 25 categories: Unit Operation Set Up (i.e., equipment preparation), Unit Operation Execution (i.e., equipment usage), and Unit Operation Clean Up (i.e., equipment clean up). Tasks associated with Unit Operation Execution can be said to be on the critical path of the PTL and usually involve manipulation of the product in preparation for the next unit operation in the process procedure.

Unit Operation Set Up Tasks (SUTs) are performed before Unit Operation Execution Tasks
 30 in order to prepare equipment for the Unit Operation Tasks that are on the critical path of the PTL.

Generally, SUTs can be performed any time before the first Unit Operation Execution task is scheduled to be started based on the availability of the product from the previous unit operation. However, SUTs cannot be back scheduled to the extent that they interfere with completion of the previous usage cycle for the respective set of equipment or compromise the integrity of the process or product in any way. Unit Operation Clean Up Tasks (CUTs) are required in order to clean and prepare equipment for its next use. The above definitions of the three basic tasks are important relevant to accurately defining the impact of the above design cycles and their associated offsets on task scheduling in the PTL.

An application of the offset refinement can be explained, for example, with reference to mammalian cell culture production process (see FIG. 4 described above) and microbial fermentation process (See FIG. 5 described above). Referring to FIG. 82, an example showing the harvest and initial purification steps associated with a mammalian cell culture process is presented. A mammalian cell culture process provides a good example of the use of Batch Cycles as well as Unit Operation Cycles and their respective offsets. It is based on a batch process that involves continuous or semi-continuous product synthesis with batch purification of the crude product produced by the cell culture reactor.

Because a mammalian cell culture reactor may be in production for 60-90 days, the product enriched media that the cells grow in is typically harvested either continuously or in batch harvest cycles every 1, 2 or 3 days. In each harvest cycle a fresh supply of media is fed to the reactors as the product enriched media is harvested. Thus, the mammalian cell process illustrated in FIG. 82 demonstrates how Batch Cycles and their offsets impact the generation of a consecutive PTL together with the Unit Operation Cycles and their offsets.

Referring to FIG. 83 an example showing the initial purification steps associated with a microbial fermentation process is presented. A microbial fermentation process provides a good example of the use of two types of Cluster Cycles and their respective offsets and how they and their offsets impact the generation of a consecutive PTL.

Referring again to FIG. 82, where media is batch harvested every twenty-four hours for three UC's (Unit Operation 1) and these daily harvests are pooled every 72 hours to be batch purified (Unit Operations 2-4), a base model which demonstrates the use of offsets for Batch Cycles (BC) as well as Unit Operation Cycles is present. In this case a BC is defined by unit operations 2-4 as

a subset of the process cycle defined by unit operations 1-4. The Batch Cycle Offset (BCO) in this case is 72 (3 days). Every 3 days a new batch of material is begun. In a PTL for this example, if one were to demonstrate a consecutive time line with iterative Batch Cycles, the start of the First Critical Path Task (FCPT) would have to be offset from the beginning of the FCPT from the previous BC.

5 Referring again to FIG. 83, where a cluster of three concurrent unit operations is cycled 3 times in order to "disrupt" the cells harvested from a fermentor, a concurrent or simultaneous cluster cycle is presented (Unit Operations 10305-10307). In a simultaneous cluster cycle all the unit operations in a given cluster cycle operate simultaneously versus sequentially during each cluster cycle. In this case the inlet heat exchanger, cell disruption and outlet heat exchanger all operate
10 simultaneously to each other during each Cluster Cycle. In Unit Operations 10309-10310, a sequential cluster cycle is presented where the first unit operation in the cluster completes its unit operation cycle before the next unit operation in the cluster cycle begins and so on during each cluster cycle.

Referring to FIGs. 23A-E, a PTL generated based on the design cycles defined in the Unit
15 Operation List in FIG. 82 is shown. In this PTL, there is a PTL Module (PTLM) for each unit operation cycle required to generate a consecutive time line based on the design cycle patterns defined in the Unit Operation List. Column 2302 lists the DSC for each PTLM in the sample PTL. Column 2304 lists calculations required to determine the duration of each of the calculated tasks associated with a unit operation. Column 2306 lists the duration of each task as determined by either
20 calculation or manual entry. Column 2308 lists schedule adjustment factors (SAF) to forward schedule or back schedule a task duration. Column 2310 lists the adjusted duration of a task based on the calculated duration in column 2306 and the adjustment factor in column 2308.

Column 2312 lists the finish times, in hours, for each of the SUTs. These finish times are back calculated from the FCPS time based on the task duration and SAF for each SUT (as further
25 explained below). Column 2314 lists the finish times for each of the Critical Path Tasks (CPT) associated with a unit operation. The finish times are forward calculated from the First Critical Path Task End Time (FCTPE) based on the task duration and SAF for each respective CPT (further explained below). Column 2316 lists the finish times for the CUTs associated with a unit operation. Finish times for these CUTs are calculated from the finish time of the Critical Path End Time for the
30 Current Unit Operation (CCPE) and the adjusted durations for each of the subsequent CUTs.

Column 2318 lists the calculated start time for each task in the PTL based upon the end time for the respective task in columns 2312, 2314, or 2316, and their respective task duration and SAFs from columns 2306 and 2308, respectively. Column 2320 lists the calculated end time for each task in the PTL based on the end times determined in columns 2312, 2314 or 2316.

5 Referring to FIG. 85, a high level flow chart that illustrates the method for determining the impact of design cycle offsets on the Current Critical Path Start Time (CCPS) for a respective Unit Operation Cycle in the PTL is shown. In Step 8502, the Batch Cycle Iteration Field (BCIF) for the PTLM (DCS Field 2) is evaluated to determine if the current unit operation sequence number is the start unit operation for a Batch Cycle Iteration as defined in column 8220 in FIG. 82. If it is, the
10 CCPS time for the new Batch Cycle Iteration is calculated from the start time from the previous BC plus the BCO. If not, the BC test is ended and the cluster cycle conditions for the current unit operation are then evaluated in Step 8504.

Referring to FIG. 86, the evaluation in step 8502 is further illustrated. The BCIF for the Current Unit Operation in Step 8602 is evaluated in step 8604. If the BCIF for the Current Unit
15 Operation is not greater than one, the BC test is ended (Step 8606) and the Cluster Cycle Test is performed. If the BCIF is greater than one, the Batch Cycle Start Unit Operation (BCSO) is obtained from column 8222 from FIG. 82 (Step 8608). The BCIF is evaluated in Step 8610 to determine if it is equal to the BCSO. If the BCIF is not equal to the BCSO, the Batch Cycle Test is ended in Step 8606 and the Cluster Cycle Test is performed. If the BCIF is equal to the BCSO,
20 then the BCO is obtained from Column 8226 in FIG. 82 (Step 8612). In Step 8616, the BSO is evaluated to determine if it is greater than zero. If the BCO for the Current Unit Operation is not greater than zero, the Batch Cycle Test is ended in Step 8606 and the Cluster Cycle Test is Performed. Otherwise, the CCPS is set equal to the PCPS plus the BCO (Step 8618). The resulting value from FIG. 86 is then stored for further evaluation in Step 8508.

25 A Cluster Cycle occurs when a set of two or more Unit Operations cycle together prior to the next steps in the manufacturing procedure within a BC. In some cases the Unit Operations in the Cluster Cycle follow each other sequentially where the CCPS of a subsequent Unit Operation in a CC follows the End Time for the Last Critical Path Task of the previous Unit Operation (PCPE) in the UC. An example of this type of CC is found in FIG. 83 in a sample case of the initial
30 purification stage of a Microbial Fermentation Process. In this sample case, the Inclusion Body

Wash steps in Unit Operations 10309 - 10310 are repeated twice before continuing with Unit Operation 10311. The Dilution Step is completed before the Centrifugation Step is started. After Unit Operation 10310 is completed Unit Operations 10309 - 10310 are repeated a second time in the same sequential manner before continuing with the next unit operation 10311, thus completing the
5 second cluster cycle. In other CC cases the Unit Operations subsequent to the first Unit Operation in a CC occur concurrently to the first Unit Operation in the CC. In this latter case the CCPS of each Unit Operation in the CC that is subsequent to the first Unit Operation in the CC is set equal to the Critical Path Start Time of the First Unit Operation in the CC. An example of this type of CC is also found in FIG. 83. More specifically, the Cell Disruption Steps in Unit Operations 10305 - 10307
10 are repeated three times before continuing with Unit Operation 10308. In this case Unit Operations 10306 and 10307 each occur simultaneously to the first (10305). In other words, all three Unit Operations in the Cluster Cycle share the same CCPS.

Step 8504 of FIG. 85 illustrates a CC test being performed to determine if the current Unit Operation in the PTL is the start of a new CC. In Step 8504, the Cluster Cycle Iteration Field
15 (CCIF) for the current unit operation (DCS Field 3) is evaluated to determine if the Current Unit Operation sequence number in column 8302 is the start unit operation for a Cluster Cycle Iteration as defined in column 8314 in FIG. 83. If it is, the CCPS time for the new Cluster Cycle Iteration is calculated from the start time from the previous CC plus the Cluster Cycle Offset (CCO) from column 8318 as further explained below.

Referring to FIG. 87, the CC test in step 8504 is further illustrated. The CCIF for the current Unit Operation in Step 8702 is evaluated in Step 8704. If the CCIF is not greater than one, the CC test is ended in step 8706 and the Unit Operation Cycle Test is performed as in Step 8506. If the CCIF is greater than one, the Cluster Cycle Start Unit Operation (CCSO) is obtained from column 8314 in FIG. 83 (Step 8708). In Step 8710, the CCIF is evaluated to determine if it is equal to the
25 CCSO. If the CCIF is not equal to the CCSO the CC test is ended in Step 8706 and the Unit Operation Cycle Test is performed. If the CCIF is equal to the CCSO, then CCO for the Current Unit Operation is obtained from column 8318 (Step 8712). In step 8714 the CCO is evaluated to determine if it is greater than zero.

If the CCO is greater than zero, CCPS is set equal to Critical Path Start for the Previous
30 Cluster Cycle plus the CCO (Step 8716). If the CCO is not greater than zero, the CCO is evaluated

in Step 8718 to determine if it is equal to "S" meaning that the current Unit Operation is to start simultaneously (concurrently) to the first Unit Operation in the current Cluster Cycle. If the CCO is not equal to "S", the CC test is ended in Step 8706 and Unit Operation Cycle Test is performed. Otherwise, the CCPS is set equal to the Critical Path Start for the Previous Cluster Cycle (Step 5 8720). The resulting value from FIG. 87 is stored for further evaluation in Step 8508.

Step 8506 of FIG. 85 illustrates a UC test being performed after a CC test. In Step 8506, the Unit Operation Cycle Iteration Field (UCIF) for the current unit operation (DCS Field 4) is evaluated to determine if it is greater than one. If it is not, the Unit Operation Cycle Test ends. If it is, the CCPS time for the new Unit Operation Cycle Iteration is calculated from the start time from the 10 previous UC plus the Unit Operation Cycle Offset (UCO) as further defined below. Otherwise the CCPS time for the current Unit Operation continues from the PCPE of the previous Unit Operation.

Referring to FIG. 88, the evaluation in step 8506 is further illustrated. In Step 8802, the UCIF for the current Unit Operation is obtained. In Step 8804 it is evaluated to determine if it is greater than one. If the UCIF is not greater than one, the Cycle Offset Test ends as indicated by Step 15 8806. If the UCIF is greater than one, then the UCO for the Current Unit Operation in column 8207 is obtained (step 8808). In step 8810, the UCO is evaluated to determine if it is greater than zero. If the UCO is greater than zero, CCPS is set equal to Critical Path Start for the Previous Unit Operation Cycle plus the UCO (Step 8812). If the UCO is not greater than zero, the UCO is evaluated in Step 8814 to determine if it is equal to "S" meaning that the current Unit Operation is 20 to start simultaneously (concurrently) to the previous Unit Operation. If UCO is not equal to "S", the Unit Operation Cycle Test is ended (Step 8806). Otherwise, the CCPS is set equal to PCPS (Step 8816). The resulting value from FIG. 88 is stored for further evaluation in Step 8508.

Step 8508 of FIG. 85 evaluates the results of the above three Cycle Offset Tests to see if there is a positive result from any of them, indicating that the current unit operation is the beginning 25 of an iteration of one of the three levels of design cycles to which a design cycle offset applies. If there is not a positive result, CCPS is set equal to PCPE (Step 8510). If there is a positive result CCPS is set equal to the latest start time produced by the three tests (Step 8512).

FIG. 89 further illustrates Steps 8508-2412 of FIG. 85. In Steps 8902, 8904 and 8906 the Design Cycle Test Results from the Batch Cycle Test, Cluster Cycle Test and Unit Operation Cycle

Test are obtained, respectively. In Step 8908, these obtained values are evaluated to find the maximum CCPS value (MCCPS). In step 8910, the MCCPS value is evaluated to determine if it is greater than zero. A MCCPS value equal to zero in Step 8908 indicates that the current unit operation is not a start unit operation for any design cycle iteration to which a design cycle offset applies. Therefore the CCPS time for the current unit operation in this case is PCPE (Step 8912). A MCCPS value greater than zero indicates that the current unit operation is the start unit operation for at least one design cycle iteration to which an offset greater than zero applies at the respective design cycle level. Therefore the CCPS time for the current unit operation in this case is equal to MCCPS from Step 8908. Note that the Design Cycle Tests illustrated in FIGs. 85-31 only impact the PTL if the Current Unit Operation (CUO) is the Start Unit Operation (SUO) for an iteration of at least one of the above design cycles and the offset of that design cycle is greater than zero or equal to "S". Otherwise the CCPS starts at PCPE even if the CUO is the SUO for a given Design Cycle.

Once the accurate CCPS has been determined via the above procedure, the CCPS times for each of the Design Cycle levels needs to be updated to be referenced by the Design Cycle Check mechanism for the next PTLM in the PTL as shown in Step 8514 of FIG. 85. This update mechanism is dependent on the current PTLM being the SUO of a respective Design Cycle set and the number of cycles for a respective Design Cycle level being greater than one. This update mechanism does not depend on there being an Offset Value greater than zero associated with the respective Design Cycle, as does the above Design Cycle Check mechanism.

FIG. 90 further illustrates the procedure for updating the CCPS for the current Batch Cycle for the current PTLM. The BCIF is obtained in Step 9002 and evaluated in Step 9004. If the BCIF is not greater than one, the current PTLM is not the start of a new Batch Cycle because there are no reiterating Batch Cycles defined for the current PTL in the Unit Operations List (FIG. 82, Column 8220). Therefore, the Start Time for the CCPS for the current Batch Cycle (CBCS) is set equal to the CBCS for the previous Unit Operation (Step 9006). If BCIF is greater than one, the BCIF is further evaluated in Step 9008 to determine if it is equal to the BCSO. If the BCIF is not equal to the BCSO, the current Unit Operation is not the Start Unit Operation for a new iteration of a Batch Cycle. Therefore, the CBCS is set equal to CBCS for the Previous Unit Operation (Step 9006). If the BCIPF is equal to the BCSO, the current Unit Operation is the Start Unit Operation for a new

iteration of a Batch Cycle and CBCS is set equal to the CCPS for the Current PTLM as determined by the procedures illustrated in FIGs. 86 - 89.

FIG. 91 further illustrates the procedure for updating the CCPS for the current Cluster Cycle for the current PTLM. The CCIF is obtained in Step 9102 and evaluated in Step 9104. If the CCIF is not greater than one, the current PTLM is not the start of a new Cluster Cycle iteration because there are no reiterating Cluster Cycles defined for the current PTL in the Unit Operations List (FIG. 82, Column 8212). Therefore, the Start Time for the CCPS for the current Cluster Cycle (CCCS) is set equal to the CCCS for the previous Unit Operation (Step 9106). If CCIF is greater than one, the CCIF is further evaluated in Step 9108 to determine if it is equal to the CCSO. If the CCIF is not equal to the CCSO, the current Unit Operation is not the Start Unit Operation for a new iteration of a Cluster Cycle. Therefore, the CCCS is set equal to CCCS for the Previous Unit Operation (Step 9106). If the BCIPF is equal to the CCSO, the current Unit Operation is the Start Unit Operation for a new iteration of a Cluster Cycle and CCCS is set equal to the CCPS for the Current PTLM as determined by the procedures illustrated in FIGs. 86 - 89.

FIG. 92 further illustrates the procedure for updating the CCPS for the current Unit Operation Cycle for the current PTLM. The UCIF is obtained in Step 9202 and evaluated in Step 9204. If the UCIF is not greater than one, the current PTLM is not the start of a new Unit Operations Cycle iteration because there are no reiterating Unit Operations Cycles defined for the current PTL in the Unit Operations List (FIG. 82, Column 8212). Therefore, the Start Time for the CCPS for the current Unit Operations Cycle (UCCS) is set equal to the UCCS for the previous Unit Operation (Step 9206). If UCIF is greater than one, the CCCS is set equal to the CCPS for the Current PTLM as determined by the procedures illustrated in FIGs. 86 - 89.

After the accurate CCPS has been determined for a PTLM and the CCPS for each of the Design Cycle Levels has been updated, the Task Start/Stop Times for each Critical Path Task (CPT) for the Current Unit Operation is calculated as illustrated in Step 8516. FIG. 93 further illustrates the procedure for determining the Task Start/Stop Times for each CPT for the Current Unit Operation. In Step 9302 the CCPS is obtained for the current PTLM via the procedure illustrated in Steps 8502-2412. In Step 9304 the duration of the First CPT (FCPT) is obtained from the calculations illustrated in FIG. 84, Column 8404. In Step 9306 the SAF is entered manually by the user to provide the user a means of delaying (or starting earlier) the start of a CPT. The SAF can be

used to manually adjust the PTL in order to start and end tasks at more favorable times with respect to shift scheduling of labor resources and equipment utilization. For example, if a task is scheduled by automatic PTL calculation to end during a night shift when no staffing is present, and staffing is required to end the task and/or start the following task on the PTL, the SAF can be used to delay the
5 start of a Critical Path Task such that the end of the task occurs when staffing will be present as required. The use of the SAF, as well as its limits of use, is further discussed below.

In step 9308 the CCPS for the current PTLM is added to the duration and the SAF of the FCPT to determine the end time of the FCPT (FCPTE). The present embodiment focuses on the determination of task end times from which the start time is back calculated. Alternatively, the
10 FCPT Start time can be determined first by adding the SAF to the CCPS for the current PTL. In this latter case the FCPTE is calculated by adding the duration for the FCPT to this start time. The former method was chosen for this example because the end time of a CPT task is generally the focus of attention when optimizing a PTL. Generally, the SAF for all Critical Path Tasks is usually greater than or equal to zero. If the SAF for a CPT is less than zero, the start time for the CPT may
15 conflict with the end time for the previous CPT.

For example, if the transfer of a product from a "product hold vessel" to a "product mix vessel" is defined as CPT 1, and the mixing of the product in the mix vessel is defined as CPT 2, the start/end times for CPT 2 cannot be back scheduled such that the start time for CPT 2 begins before the transfer of the product from CPT 1 is complete. However, there may be instances when it is
20 preferable for the start time for CPT2 to begin before CPT 1 is completed. Such an example may involve the cooling or heating of product in a product mix vessel associated with CPT 2. If the start of the cooling or heating cycle for the product is associated with CPT 2, the heating or cooling cycle may need to be started after the product transfer has started and before the product transfer is complete. In this case the SAF can be a negative value. However, in general, the SAF is used to
25 delay the start/end of a CPT from the completion time of the previous CPT, provided the delay does not conflict with use of the unit operation resources for another scheduled event or comprise the process or product in any other way.

Returning to FIG. 93, in Step 9314, the end time for a subsequent CPT is similarly determined by adding the duration (Step 9310) and SAF (Step 9312) for the subsequent CPT to the

end time from the previous CPT for a given PTLM. The start time for the subsequent CPT can then be back calculated from the end time by subtracting the sum of the duration and SAF for the given subsequent task. As in the case of the FCPT, the start time for the subsequent CPT can be alternatively calculated first by adding the SAF to the end time for the previous CPT within the

5 PTLM. In this case, the end time for the subsequent CPT is then calculated by adding the duration for the subsequent CPT to this sum. The procedure for determining the Start/Stop time for a subsequent CPT in Steps 9310 to 9314 is repeated for each subsequent CPTs associated with a given PTLM, thereby generating a critical path time line for the current PTLM.

Referring to FIG. 94, the procedure for determining the Task Start/Stop Times for each SUT

10 for the Current Unit Operation is further illustrated. The FCPTE for the Current PTLM is obtained from Step 9310 for the current PTLM. In Step 9402, the duration of the Last SUT (SUTL) is obtained from the calculations illustrated in FIG. 84, Column 8404. In some cases, the duration of SUTL will be entered manually by the user rather than calculated. In Step 9404, the Forward/Batch Schedule Adjustment Factor (SAF) for the SUTL is entered manually to provide the user a means

15 of starting the SUT earlier. In most cases the SAF for all SUTs will be less than or equal to zero, implying that the SUT will start in time to be completed before the next task in the PTL begins or will start earlier than the minimum start time. If the SAF for a CPT greater than zero, the start time for the CPT may conflict with the end time for the previous CPT.

In step 9406, the duration of the FCPTE for the current PTLM is subtracted from the FCPTE

20 and added to the SAF for the SUTL to determine the end time of the SUTL. As previously stated, the present embodiment focuses on the determination of task end times from which the start time is back calculated. Alternatively, the SUTL Start Time can be determined by subtracting the duration of the FCPTE and SUTL from the FCPTE and adding the SAF to the result. In this latter case, the end time for the SUTL is calculated by adding the duration for the SUTL and SAF to its

25 start time. The former method was chosen for this example because the end time of a SUT task is generally the focus of attention when optimizing a PTL.

In Step 9412, the end time for a previous SUT is similarly determined by subtracting the duration of the current SUT from (Step 9408) from the end time for the current SUT and adding the result to the SAF (Step 9410) for the previous SUT. The start time for the previous SUT can then

30 be back calculated from its end time by subtracting its duration from its end time. As in the case

of the SUTL, the start time for the previous SUT can be alternatively calculated first by subtracting the duration of the current SUT and previous SUT from the end time of the current SUT and adding the SAF for the previous SUT to the result. In this case, the end time for the previous SUT is then calculated by adding the duration for the previous SUT to this sum. The procedure for determining the Start/Stop time for a previous SUT in Steps 9408 to 9412 is repeated for each previous SUT associated with a given PTLM, thereby generating a critical path time line for the current PTLM.

Referring to FIG. 95, the procedure for determining the Task Start/Stop Times for each CUT for the Current Unit Operation is further illustrated. The CCPE for the Current PTLM is obtained in Step 9502. In Step 9504, the duration of the First CUT (CUTF) is obtained from the calculations illustrated in FIG. 84, Column 8404. In some cases the duration of CUTF will be entered manually by the user rather than calculated. In Step 9506, the SAF for the CUTF can be altered manually from its default of zero to provide the user a means of delaying the start of the CUT. In most cases the SAF for all CUTs will be greater than or equal to zero. This implies that the CUT will start when the last CPT for a given PTLM is completed (SAF for CUT is set equal to zero) or sometime after CCPE (SAF for CUT is greater than zero) provided that all CUTs associated with a PTLM are completed before the next use cycle of the equipment and resources associated with the current PTLM. If the SAF for a CPT is less than zero, the start time for the CPT may conflict with the end time for the last CPT (or previous CUT). In step 9508, the CCPE for the current PTLM obtained in Step 9502 is added to the duration and SAF for the CUTF to determine the end time of the CUTF. As previously stated, the present embodiment focuses on the determination of task end times from which the start time is back calculated. Alternatively, the CUTF Start Time can be determined first by adding the SAF to the CCPE. In this latter case the end time for the CUTF is calculated by adding the duration for the CUTF to its calculated start time. The former method was chosen for this example because the end time of CUT task is generally the focus of attention when optimizing a PTL.

In Step 9514, the end time for a subsequent CUT (CUTS) is similarly determined by adding the duration (Step 9510) and SAF (Step 9512) for the CUTS to the end time from the current CUT for a given PTLM. The start time for the CUTS can then be back calculated from the end time by subtracting the duration of the CUTS from its end time. As in the case of the CUTL, the start time for the CUTS can be alternatively calculated first by adding the SAF to the end time for the current

CUT within the PTLM. In this latter case, the end time for the CUTS is then calculated by adding the duration for the previous CUT to this sum. The procedure for determining the Start/Stop time for a CUTS in Steps 9508 to 9512 is repeated for each CUTS associated with a given PTLM, thereby generating a critical path time line for the current PTLM. The Process Start Time (PST) for a PTL is entered manually by the user and provides the start point for all of the above time line calculations. The first PTLM in a PTL takes the PST as the CCPS to begin the PTL. Once the CCPS for the first PTLM has been entered, it is possible to calculate start and end times of all the CPTs, as well as the SUTs and CUTs associated with the first PTL. Subsequently, the start and end times of the CPTs, SUTs and CUTs for all subsequent PTLMs can be determined based on the above procedure.

2.0 Solution Preparation Scheduling Module

The preferred embodiment of the present invention is a computer based system and method for the simulation, modeling and scheduling of batch process solution preparation. The preferred embodiment is based on a method for generating scheduling information which accurately defines the complex manufacturing operations of solution preparation in batch manufacturing processes. This scheduling capability system allows the definition of manufacturing costs and systems in a more detailed and accurate manner than previously possible. As a result, this invention allows the rapid and accurate evaluation of numerous batch manufacturing alternatives in order to arrive at an optimal process design early in a facility development project. In so doing the invention minimizes project cost over runs which result from inaccuracies that can carry forward from the early stages of design into construction. The invention also allows the accurate scheduling of solution preparation activities in an operating manufacturing plant, including the scheduling of resources required by solution preparation such as labor, reagents, disposables, reuseables, utilities, equipment maintenance & calibration, etc..

The object of the solution preparation scheduling module is to assign each solution to a solution preparation vessel and to generate a solution preparation schedule for each solution preparation vessel. Scheduling solution preparation in each solution preparation vessel allows the biopharmaceutical production process designer to manage, predict and optimize solution

preparation vessel inventory, equipment cost, utility requirements, clean and preparation and other solution preparation associated activities.

FIG. 13 is a flow chart providing an overview of the process for scheduling and simulating solution preparation in a biopharmaceutical production process. Step 1302 determines the solution preparation time for each solution preparation vessel. A solution preparation vessel is a vessel used for the preparation of solution used in the biopharmaceutical production process. In the preferred embodiment, each type of solution preparation vessel used in the biopharmaceutical production process has an associated solution preparation time. The solution preparation time is the amount of time it takes to prepare solution in the solution preparation vessel. Preparation of one solution preparation vessel's volume of solution is called a solution preparation cycle. Each solution preparation vessel has associated solution preparation parameters. Solution preparation parameters describe the amount of time necessary to complete various steps in the solution preparation process.

Step 1304 assigns the solutions in the biopharmaceutical production process to particular solution preparation vessels. Solutions are assigned to particular vessels in order to schedule and determine the load on the solution preparation vessels. Step 1304 includes the procedure of determining the total volume of each solution needed for the biopharmaceutical production process and assigning it to a preparation vessel of the appropriate size. Large volume solutions can be prepared in smaller multiple solution preparation cycles and pooled to yield a higher volume batch of solution. Conversely, smaller volume solutions can be batch prepared in larger preparation volumes to accommodate multiple process cycles provided the shelf life of these solutions allow longer storage times.

Step 1306 determines the calculated start date and the next preparation date of each solution. The calculated start date for the preparation of a solution is the date which solution preparation should begin in order to have the solution ready for use in the biopharmaceutical process. The calculated start date takes into account the amount of time necessary to prepare the solution, and other lead-time factors necessary for preparation of solution. The next preparation date is the earliest date that a solution will be prepared after its calculated start date. The next preparation date is determined by adding the periodicity of solution preparation to the calculated

start date. The periodicity of solution preparation is how often each solution must be prepared in order to sustain the biopharmaceutical production process.

Step 1308 determines the earliest solution preparation date for each solution preparation vessel for a given process cycle. Since each solution has been assigned to a solution preparation vessel, and the calculated start dates for each solution have been determined, step 1308 determines the earliest calculated start date for each solution preparation vessel. The earliest calculated start date associated with a solution preparation vessel is the date which the first solution is prepared in the vessel for a given process cycle. The earliest calculated start date associated with a solution preparation vessel identifies the point in the process cycle by which the preparation vessel must be available.

Step 1310 determines the latest next preparation date for each solution preparation vessel. The latest next preparation date for each solution preparation vessel is the date that a solution preparation vessel is last used for solution preparation to support a given process cycle. Based on the solution to solution preparation vessel assignments determined in step 1304, the earliest calculated start date for each solution and the next preparation dates for each of the solutions determined in step 1306, step 1310 determines the latest next preparation date for each solution preparation vessel. The earliest calculated start date and the latest next preparation date associated with a solution preparation vessel define the usage boundaries of the solution preparation vessel in the process cycle. The loading of a solution prep vessel can be evaluated during the time between the earliest calculated start date and the latest next preparation date. In the case where the usage boundary is set by a solution which is batch prepared to accommodate multiple process cycles, the usage boundary of a tank includes these multiple process cycles. Therefore the loading on a solution preparation vessel in this instance will also account for solutions from multiple process cycles.

The duration of time between the first biopharmaceutical production process activity related to a given process and the last biopharmaceutical production process activity related to that process may be called a manufacturing cycle (i.e., multiple process cycles define a manufacturing cycle). In the case where an activity, such as the preparation of a solution, accommodates multiple process cycles, a manufacturing cycle consists of multiple process cycles. In the case where all the activities associated with a process only accommodate one process cycle a

manufacturing cycle consists of only one process cycle. Therefore manufacturing cycles may consist of one or more process cycles with their related support activities.

Step 1311 calculates the use duration for each solution preparation vessel. The use duration for each solution preparation vessel is the time that a solution preparation vessel is occupied with the preparation of solution for a manufacturing cycle. For example, when multiple solutions are assigned to a single solution preparation vessel, the use duration for the solution preparation vessel is determined based on the earliest calculated start date and the latest next preparation date for all of the solutions assigned to the solution preparation vessel. The total number of hours the solution preparation vessel is occupied can be calculated from the use duration (days) and the number of shift hours per day for the particular manufacturing cycle (e.g., single shift operation would normally be 8 hours per day).

Step 1312 calculates the cumulative solution preparation time for each solution preparation vessel. The cumulative solution preparation time is the amount of time a solution preparation vessel is occupied with the preparation of solutions in a biopharmaceutical manufacturing cycle.

Step 1312 calculates the cumulative solution preparation time for each solution preparation vessel based on:

- 1) the solutions assigned to a particular vessel;
- 2) the prep vessel use duration;
- 3) the duration of a process cycle;
- 4) the number of preps of a solution per process cycle; and
- 5) solution preparation times.

For example, if five solutions are to be prepared in a particular solution preparation vessel each requiring two preparations per process cycle, process cycle durations of seven days, solution preparation times of three hours, during a use duration of fourteen days, the cumulative solution preparation time for the solution preparation vessel would be sixty hours over a two week period.

Step 1314 determines the percent utilization of each solution preparation vessel. The percent utilization of each solution preparation vessel is the fraction of the use duration that the solution preparation vessel is actually engaged in the preparation of solution, or the cumulative solution preparation time. The percent utilization is determined based on the use duration,

cumulative solution preparation time and the number of hours per solution prep shift for the process cycle. For example, if the use duration for a solution preparation vessel is fourteen days, and there are eight shift hours per day, then the solution preparation vessel has a total availability of one hundred twelve hours. If, as calculated above, the cumulative solution preparation time
5 for the solution preparation vessel is sixty hours, then the percent utilization of the solution preparation vessel is approximately fifty-four percent. The percent utilization of each solution preparation vessel is determined in step 1314 so that the biopharmaceutical production process planner is able to gauge the level of utilization of the solution preparation equipment and make any adjustments in the solution preparation equipment pool or production cycles.

10 Step 1316 generates the initial shift schedule for each solution preparation vessel. The initial shift schedule is a daily schedule of solutions to be prepared in a particular solution preparation vessel. Step 1316 generates the initial shift schedule based on the calculated start date for each solution, the periodicity of solution preparation for each solution and the solution to solution preparation vessel assignment.

15 Step 1318 back schedules solution preparation procedures that do not fit in the shift schedule and checks for system capacity problems. Back scheduling is the process of rescheduling solution preparation cycles for previous days or time slots. The initial shift schedule is generated regardless of the number of hours a solution preparation vessel is occupied for a particular day. For example, the initial shift schedule may have a particular solution preparation vessel scheduled
20 for fourteen hours of solution preparation. In a biopharmaceutical production process that operates sixteen hours a day, all of the solutions scheduled for the solution preparation vessel can be accommodated. If, however, the biopharmaceutical production process operates only eight hours a day, not all of the required solutions may be prepared on the scheduled date. Step 1318 back schedules to earlier days those solution preparation cycles that cannot be completed on the
25 initially scheduled day. The scheduling of a back scheduled solution preparation cycle into an available shift is performed according to the priority of the oldest back scheduled date for all available back scheduled solutions. The end result of step 1318 is to generate a final shift schedule for each prep vessel which assigns the appropriate solutions to that vessel and schedules out the preparation of each solution according to shift capacity, the duration of each prep assigned
30 to that shift.

Step 1320 generates a time line for the operation of each solution prep vessel and its associated equipment according to the shift assignments in the final shift schedule and the durations associated with each solution prep step in the solution prep procedure table. Based on this time line resources requirements for labor, reagents, disposables, reusables, utilities, maintenance, etc., can be accurately scheduled.

FIG. 14 further illustrates step 1302, determining the solution preparation time for each solution preparation vessel. Step 1302 begins at step 1420 determining the setup time for a solution preparation vessel. Step 1420 compares a list of solution preparation vessels 1402 that are available for use in the biopharmaceutical production process and their associated solution preparation vessel identifiers with a master list of solution preparation vessel identifiers and their associated set up times 1410. Solution identifiers and solution preparation vessel identifiers are keys or tags that identify individual solution preparation vessel and solution types. Examples of solution preparation vessel set up times are illustrated in FIG. 15, column 1410. List of solution preparation vessels 1402 includes the minimum/maximum working volumes for each vessel, as well as the particular tasks associated with the solution preparation vessel and any process equipment necessary to complete solution preparation. The solution preparation tasks and equipment may be included in the total solution preparation time 1428 for use in equipment preparation and scheduling.

Next, step 1408 determines the water collection time for each preparation vessel. The water collection time is the amount of time necessary to fill the maximum working volume 1406 of the solution preparation vessel at the water collection rate 1404. Water collection rate 1404 is the rate at which the solution preparation vessel can be filled. Different solution preparation vessels have different water collection rates, depending on their specific water collection hardware. Step 1408 estimates the water collection time for each solution preparation vessel based on its maximum working volume 1410 and the water collection rate 1404. In the preferred embodiment, the volume of water to be collected is assumed to be the preparation vessel maximum working volume 1406. In alternative embodiments, the volume of water to be collected can be the actual volume of solution prepared in the solution preparation cycle. Examples of water collection rate 1404, maximum working volume 1406 and water collection time 1502 are illustrated in FIG. 15, columns 1404, 1406 and 1502, respectively.

Step 1414 defines the weigh and mix times associated with each solution preparation vessel. Weigh and mix time 1416 is the time required to weigh, mix and adjust the components of a solution. Preparation vessel identifiers 1402 are matched with the associated preparation vessel weigh and mix time 1416. The weigh and mix time 1416 associated with each solution preparation vessel in the biopharmaceutical process is thereby assigned to the associated solution preparation vessel identifier 1402. The default weigh and mix time variables can be manipulated by the process designer. Examples of weigh and mix time 1416 are illustrated in FIG. 15, column 1416.

Next, step 1418 determines the time required to filter the solution in a preparation vessel. The time required to filter the solution in a preparation vessel is the amount of time post-preparation filtering and transfer of the prepared solution out of the solution preparation vessel requires. Step 1418 calculates the time required to filter the solution in a preparation vessel based on preparation vessel identifier 1402, preparation vessel maximum working volume 1406, filtration flux rate 1424 and surface area of filtration media 1412. In the preferred embodiment, the volume of solution to be filtered is assumed to be the preparation vessel maximum working volume 1406. In alternative embodiments, the volume of solution to be filtered can be the actual volume of solution prepared in the solution preparation cycle. The surface area of the filtration media 1412 is the area of the filtration media used to filter the solution as it is transferred out of the solution preparation vessel. Filtration flux rate 1424 is the rate per unit area that the solution is can be filtered through the filtration media. Examples of filtration flux rate 1424 and surface area of filtration media 1412 are illustrated in FIG. 15, columns 1424 and 1412, respectively.

Step 1426 calculates the adjusted filtration time. The adjusted filtration time is the filtration time as determined in step 1418 multiplied by the filtration delay factor 1430. Filtration delay factor 1430 is based on the additional filtration time typically required to manipulate solution storage vessels on a fill line. Step 1426 calculates the adjusted filtration time by multiplying the filtration time calculated in step 1418 by the filtration delay factor 1430. FIG. 15, column 1430 shows exemplary values for filtration delay factor 1430.

Step 1432 determines clean in place and steam in place durations associated with each solution preparation vessel. Clean in place duration 1422 and steam in place duration 1434 are the durations of the cleaning procedures necessary to prepare a solution preparation vessel for use

in the next solution preparation cycle. Step 1432 matches preparation vessel identifiers 1402 with clean in place duration 1422 and steam in place duration 1434 to determine the clean in place duration 1422 and steam in place duration 1434 times associated with each of the solution preparation vessel used in the biopharmaceutical production process. FIG. 15, columns 1422 and 1434 illustrate exemplary values for clean in place duration 1422 and steam in place duration 1434, respectively.

Step 1436 calculates total solution preparation time 1428 for each preparation vessel by summing the time values calculated in steps 1420, 1408, 1414, 1418, 1426 and 1432. Total solution preparation time 1428 represents the amount of time required to prepare the maximum working volume 1406 of solution in a particular solution preparation vessel. It should be noted, however, that one of ordinary skill could expand the calculation of total solution preparation time 1428 to include additional steps, factors or parameters other than those described herein. Such expansion would allow the present invention to calculate the total solution preparation time 1428 for a solution preparation vessel more accurately, or to include additional factors in the calculation. In addition, the calculation of total solution preparation time 1428 for a solution preparation vessel could also be adjusted to accommodate solution preparation working volumes which are less than the maximum solution preparation working volumes for a given solution prep vessel. Column 1428 of FIG. 15 provides exemplary values for total solution preparation time 1428.

FIG. 15 shows an exemplary list of solution preparation parameters. Examples of such parameters are minimum working volume 1402, maximum working volume 1406, set up time 1410, water collection rate 1404, water collection time 1502, weigh and mix time 1416, square area of filter media 1412, volume per unit of filter area per hour 1424 and post-solution preparation and cleaning procedure duration 1422, 1434.

Minimum working volume 1402 and maximum working volume 1406 are the minimum and maximum volumes of solution a solution preparation vessel can prepare. Set up time 1410 is the amount of time necessary to prepare a solution preparation vessel for the solution preparation process. Water collection time 1404 is the time necessary to fill the solution preparation vessel with the maximum working volume 1406 of water. Weigh and mix time 1416 is the time necessary to weigh and mix the ingredients of a solution in a particular solution

preparation vessel. Square area of filter medium 1412 is the area of the filter associated with a particular solution preparation vessel. Volume per unit of filter area per hour 1424 is the flux rate per unit of filter area associated with a particular solution preparation vessel. Post solution preparation and cleaning procedure duration 1422 and 1434 are the times associated with
5 preparing the solution preparation vessel after the preparation of a batch of solution.

FIG. 16 further illustrates step 1304, assigning the solutions required by the biopharmaceutical production process to particular solution preparation vessels. In order to schedule solution preparation cycles, each solution must be assigned to a solution preparation vessel. Step 1304 begins with step 1602. Step 1602 sets the preparation cycles per batch for a
10 solution to be prepared. Preparation cycles per batch 1608 are the number of times a solution is prepared in a solution preparation vessel to support one product batch cycle. For example, if one-hundred and fifty liters of solution 101 is required to make a batch of product in a biopharmaceutical production process and the solution is to be prepared in a fifty liter solution preparation vessel, solution 101 may be prepared in three preparation cycles per batch of fifty
15 liters each, yielding a 150 liter batch of solution 101. Alternatively, solution 101 may be prepared in four preparation cycles per batch of thirty-seven and one-half liters each in a solution preparation vessel of at least thirty-seven and one-half liters. In the preferred embodiment, preparation cycles per batch 1608 of solution is initially set by the designer. Preparation cycles per batch 1608 will affect values throughout the solution preparation scheduling module and the
20 solution preparation procedure as a whole. The number of preparation cycles per batch 1608 for each solution will dictate the size of a solution preparation vessel and the time required to prepare a batch of solution.

Step 1606 determines the number of days per solution preparation cycle 1610 for each of the solutions involved in the biopharmaceutical production process. The number of days per
25 solution preparation cycle 1610 is determined from preparation cycles per batch 1608 and days per batch cycle 1604. The batch cycle time is the amount of time required to produce one batch of product. Days per batch cycle 1604 is the number of days between successive batches of product. The number of days per preparation cycle 1610 is the number of days between the beginnings of each solution preparation. Dividing the number of days per batch cycle by the
30 preparation cycles per batch 1608 yields the number of days per preparation cycle 1610. For

example, if one-hundred and fifty (150) liters of solution per batch of product is to be prepared in a solution preparation vessel with a working volume of fifty liters, the preparation cycles per batch 1608 is three. If one batch of biopharmaceutical product is produced every 6 days, the days per batch cycle 1604 is six. Given that there are three preparation cycles per batch for a particular solution, and there are six days per batch cycle, the number of days per preparation cycle 1610 is determined to be two. That is, there are two days between the beginnings of each fifty liter preparation cycle of solution.

Decision step 1612 checks the shelf life of the solution against the number of days per preparation cycle 1610. In the preparation of solutions, it is possible that the number of days per preparation cycle 1610 may exceed the shelf life of the solution. In such a situation, it is possible to have "stale" solution available for use in the biopharmaceutical production process because it has been held to long. If decision step 1612 determines that number of days per preparation cycle 1610 is greater than the shelf life, step 1304 continues at step 1602 where the number of preparation cycles per batch 1608 is adjusted (preferably increased). Adjusting the preparation cycles per batch 1608 of the solution will allow the solution preparation process designer to decrease the number of days per preparation cycle 1610 as determined in step 1606. If decision step 1612 determines that the number of days per preparation cycle 1610 is less than the shelf life of the instant solution, step 1304 continues at step 1616.

Step 1616 calculates the liters per preparation cycle of solution 1620 for each solution. Liters per preparation cycle of solution 1620 is calculated by dividing the total liters per batch for each solution 1618 by the number of preparation cycles per batch 1608 as determined in step 1602. Total liters per batch for each solution 1618 is the quantity of each solution type needed to produce a batch of product in the biopharmaceutical production process and is stored in the material balance table.

Step 1624 determines the solution preparation vessel type for the preparation of each solution. Step 1624 assigns each solution to a solution preparation vessel in step 1624, generating preparation vessel to solution assignment list 1626. Step 1624 assigns each solution to a solution preparation vessel based on the number of liters per preparation cycle of solution 1620 and preparation vessel identifier and associated volume list 1402. Solution preparation vessels are chosen from preparation vessel identifier and associated volume list 1402 in order to place liters

per preparation cycle of solution 1620 within the minimum working volume 1402 and the maximum working volume 1406 range of a solution preparation vessel. Preparation vessel to solution assignment list 1626 is a list of solutions to be prepared in the biopharmaceutical production process, and their associated solution preparation vessel.

5 Fig. 17 illustrates exemplary values of data for the present invention. Column 1618 illustrates exemplary values for the total liters per batch for each solution 1618. Column 1608 illustrates exemplary values for number of preparation cycles per batch 1608. In the instant example, all of the solutions as shown in column 1608 are prepared in one preparation cycle per batch. Column 1604 illustrates exemplary values for days per batch cycle 1604. Column 1610
10 illustrates exemplary values of number of days per preparation cycle 1610 as determined in step 1606. In the instant example, since the number of preparation cycles per batch 1608 of solution is equal to one for all of the solutions in the solution production process, the number of days per preparation cycle 1610 equals the number of days per batch cycle 1604. Column 1614 illustrates exemplary values of shelf life of solution 1614. Column 1706 illustrates exemplary values for the
15 outcome of decision step 1612 where number of days per preparation cycle 1610 is compared to shelf life of solution 1614. Column 1618 of FIG. 17 illustrates exemplary values for total number of liters per batch for each solution 1618. Since the number of preparation cycles per batch 1608 for each of the solutions is one in the instant example, the number of liters per preparation cycle of solution 1620 is equal to total liters per batch for each solution 1618.

20 Columns 1708-1728 of FIGS. 17 and 18 illustrate an exemplary solution to solution preparation vessel assignment list 1626. The tank identifiers run along the top of column 1708-1728 and the solution identifiers run along the vertical axis on the far left hand side of the tables in FIGS. 17 and 18. In FIG. 18, exemplary solution preparation vessel identifiers are placed in the columns horizontally opposed from the solution identifiers indicating that the preparation
25 vessel is assigned to that solution.

FIG. 18 illustrates exemplary preparation vessel to solution assignment list 1626. Columns 1626 illustrates preparation vessel to solution assignments. Column 1722 illustrates solution preparation vessel #108 is associated with solutions S-0107, S-0108, S-0112, S-0115, S-0117, and S-0120. Similarly, column 1724 illustrates solution preparation vessel #109 is associated with
30 solutions S-0116, S-0118, and S-0119. Column 1726 illustrates solution preparation vessel #110

is associated with solutions S-0106 and S-0114. Column 1728 illustrates solution preparation vessel #111 is associated with solutions S-0101 and S-0113.

FIG. 20 further illustrates step 1306, determining the calculated start date for preparation of each solution 2010 and the next preparation date for each solution 2022. The next preparation date 2022 is based on the calculated start date 2010 and the number of days per solution preparation cycle 1610. Step 1306 begins at step 2004, determining the calculated start date for the preparation of each solution ("calculated start date") 2010. Calculated start date 2010 is the date by which the preparation of a solution should begin in order to prepare the solution in time for use in the biopharmaceutical production process. The calculated start date 2010 is determined by calculating back from the earliest date a solution is needed 2006 in the biopharmaceutical production process and the "lead time" needed to prepare and test a batch of solution before use. In the preferred embodiment, the back calculated values are the total solution preparation time for a solution preparation vessel 1428, the number of back days to allow for a failed lot of solution 2002 and the number of hold days for solution quality assurance and quality control (QA/QC) testing 2008. If a batch of solution fails QA/QC testing, the solution will have to be prepared again, and this lead time is expressed as the number of back days to allow for a failed lot of solution 2002. The earliest date a solution is required 2006 comes directly from the process time line via the material balance table. The material balance is a list of solution formulation reagents and calculation sets, each of which is associated with a unit operation. The material balance table includes the volumes of all the process streams in the block flow diagram 704 and their constituent solution components according to the formulation of the solution. The material balance table also identifies the time that a solution is required in the manufacturing process according to the task scheduling data in the process time line 906.

After the calculated start date for solution preparation 2010 is determined, it is assigned to the associated solution and prep vessel solution assignment list 1626 resulting in a calculated start date 2010 for the preparation of each solution and its associated solution preparation vessel.

Step 2018 calculates the next solution preparation date for each solution after the calculated start date 2010 has been determined for each solution by selecting the greater of days for batch or days for preparation. Step 2018 calculates the next solution preparation date for each solution by. The next solution date is calculated in step 2018 by adding the number of days per

preparation cycle 1610 to the calculated start date for preparation of each solution assigned to a preparation vessel 2010.

FIG. 24 further illustrates step 1308, determining the earliest solution preparation start date for each solution preparation vessel in a process cycle. Step 1308 begins by determining and assigning the calculated solution preparation start dates 2010 to each solution preparation vessel in step 2402. Solution preparation vessel ("prep vessel") to solution assignment list 1626 and calculated solution preparation start date for all solutions 2010 are cross-referenced to generate calculated and assigned solution prep start dates to prep vessels 2404. Step 2406 generates the earliest solution preparation start date for each solution preparation vessel ("earliest start date") 2408. Calculated and assigned solution prep start dates to prep vessels 2404 is processed in step 2406 to determine the earliest solution preparation start date associated with each preparation vessel. Step 2406 results the earliest preparation start dates assigned to each preparation vessel 2408. This list provides the solution preparation vessels necessary for the biopharmaceutical production process, as well as the earliest date each solution preparation vessel is needed for preparation of solution in the process cycle.

FIG. 25 further illustrates step 1310, determining the latest solution preparation start date for each solution preparation vessel. Step 1310 begins by determining and assigning the next solution preparation dates to each solution preparation vessel at step 2502. A next solution preparation date is the date that a solution preparation vessel will be needed for the preparation of solution next after the earliest start date 2408. The solution preparation vessel to solution assignment list 1626 and next solution preparation date for each solution 2022, as determined in step 2018, are matched to generate a list of next solution preparation dates to each preparation vessel at step 2502. Next, step 2504 determines the latest next solution preparation start date associated with each preparation vessel 2506. The latest next solution preparation start dates are those dates associated with preparation vessels which signify the last preparation of solution procedure to occur in a particular solution preparation vessel during a process cycle.

FIG. 26 further illustrates step 1311, calculating solution preparation vessel utilization time for each solution preparation vessel 2604. Solution preparation vessel utilization time 2604 for each preparation vessel is that time during which the vessel is occupied with the preparation of solution(s) for a particular manufacturing cycle. Solution preparation vessel utilization time 2604

is the duration between the earliest preparation start date 2408 and the end of latest next solution preparation cycle. The end of latest next solution preparation cycle is calculated by adding the total solution preparation time for a solution preparation vessel 1428 to the latest next solution preparation start date for each solution preparation vessel 2506, which results in the date when the solution preparation vessel has completed preparing solution in a process cycle. Solution preparation vessel utilization time for each solution preparation vessel 2604 is determined by comparing the earliest solution preparation start date 2408 with the sum of the latest next solution preparation start date 2506 and the total solution preparation time for each solution preparation vessel 1428.

FIG. 27 further illustrates step 1312, calculating the cumulative solution preparation time for each solution preparation vessel 2708. Cumulative solution preparation time for each solution preparation vessel 2708 is the amount of time that each preparation vessel is actually occupied with the preparation of solution. Essentially, cumulative solution preparation time is the product of the total solution preparation time for a solution preparation vessel 1428 and the number of solution preparation cycles that the solution preparation vessel is used for in the manufacturing cycle. For example, if the total solution preparation time for a solution preparation vessel is six hours per cycle, and the solution preparation vessel is used in the preparation of six cycles of solution, the cumulative solution preparation time 2708 is thirty-six hours.

Step 1312 begins by assigning a solution preparation total time for each solution preparation vessel to each preparation vessel at step 2702. Total solution preparation time for each preparation vessel 1428 from step 1302 is matched to preparation vessel to solution assignment list 1626. The lists of preparation vessels, the solutions associated therewith and their total solution preparation times are input into step 2704. Step 2704 determines the cumulative solution preparation time for each solution by multiplying the total solution preparation time 1428 for the solution preparation vessel by a solution's respective number of preparation cycles per batch 1608. Step 2704 results in the amount of time each solution preparation vessel is occupied with the preparation each particular solution. Step 2706 determines the cumulative solution preparation time for each solution preparation vessel 2708 by summing the amount of time each solution preparation vessel is actually occupied with the preparation of solution. Steps 2704 and 2706 result in the list of cumulative solution preparation times for each preparation vessel 2708.

FIG. 28 further illustrates step 1314, determining the percentage utilization of each solution preparation vessel. The percentage utilization of a solution preparation vessel is the ratio of the cumulative total solution preparation time for each solution preparation vessel 2708 to the total time that a solution preparation vessel is available for solution preparation 2802 expressed as a percentage. Determining the percentage utilization of each solution preparation vessel 2808 allows the process designer to tailor the preparation cycles per batch 1602 of each solution to maximize the utilization of the solution preparation equipment, thereby minimizing cost and maximizing efficiency. Step 1314 begins by calculating the total number of hours a solution preparation vessel is available at step 2802. The total number of hours a preparation vessel is available is the product of the solution preparation vessel utilization time 2604, as determined in step 2602, and the hours per solution preparation shift 2804. The hours per solution preparation shift 2804 is provided from in the original process design parameters for the biopharmaceutical production process. For example, if the process is designed as a two shift process, the plant would normally run sixteen hours a day, and the number of hours per solution prep shift 2804 would be sixteen.

Step 2802 multiplies the solution preparation vessel utilization time 2604 by the hours per solution preparation shift per day 2804. Step 2802 results in the number of raw hours that a solution preparation vessel is available to the biopharmaceutical production process. For example, if the solution preparation vessel utilization time 2604 is six days, and the biopharmaceutical production process is run one shift a day (eight hours), the number of hours the solution preparation vessel is available for use in the biopharmaceutical production process is forty-eight. Forty-eight is the maximum number of hours that the solution preparation vessel is available for use. If such a solution preparation vessel is actually occupied with the preparation of solution for twenty-four hours, the percentage utilization of the solution preparation vessel during its period of availability 2808 would be fifty percent.

Step 2806 calculates the percentage utilization of each solution preparation vessel. The percentage utilization 2808 is determined by comparing the total number hours a solution preparation vessel is available as calculated in step 2802 with the cumulative total solution preparation time for each solution preparation vessel 2708. By dividing cumulative total solution preparation time for each solution preparation vessel 2708 by the total number of hours a

preparation vessel is available as calculated in step 2802, percentage utilization of each preparation vessel during its period of availability 2808 is calculated, as explained in the example above.

FIG. 29 further illustrates step 1316, generating the initial shift schedule 2910. The initial shift schedule 2910 is a table of dates scheduling the preparation of solutions for use in the biopharmaceutical production process. Initial shift schedules 2910 are generated for each of the solution preparation vessels. An initial shift schedule for a solution preparation vessel contains the solutions to be prepared and their associated preparation dates, as well as the days per prep cycle. FIG. 31 is an example of an initial shift schedule. Step 1316 begins with step 2902, generating a time-line starting from the earliest start prep date of all the solutions required by the biopharmaceutical production process at step 2902. In the preferred embodiment, the time-line is incremented one day at a time, out to a date predetermined by the system designer. In alternative embodiments, the time-line and shift schedule are incremented or delimited in whichever time intervals are most convenient.

Step 2904 determines and matches solution preparation dates for each solution 2404 with the dates in the shift schedule time-line from step 2902. Matched solution preparation dates to solution preparation vessels 2404 are entered into the shift schedule time-lines for each of the solution preparation vessels. Starting from the calculated start date 2404, step 2904 enters successive preparation start dates for each solution associated with a preparation vessel based on the number of days per preparation cycle 1610. For example, if a particular solution assigned to solution preparation vessel has two days per preparation cycle, the solution is scheduled for preparation in its solution preparation vessel every two days after its calculated start date 2010. Step 2904 results in a list of solutions and associated preparation dates for each solution preparation vessel 2906.

Step 2908 enters the total number of solution preparation hours for each solution into each initial shift schedule time-line. The result is the number of preparation hours each day associated with every solution preparation in the initial shift schedule. Step 2908 matches solution preparation times for each solution preparation vessel 1428 with the dates assigned in each of the shift schedule time-lines to generate the initial shift schedule 2910. The total number of hours each solution preparation vessel is occupied with the preparation of solution each day can then be

determined by adding the number of solution preparation hours associated with each day on an initial shift schedule time-line 2910. In the preferred embodiment, the number of hours of solution preparation per day per solution preparation vessel is essentially the product of the number of solution preparation cycles and the total solution preparation time for the solution preparation vessel 1428. For example, if a solution preparation vessel has a total solution preparation time for the solution preparation vessel 1428 of five hours, and is scheduled for four solution preparation cycles, the solution preparation vessel is scheduled for twenty hours of solution preparation that day. Step 2910 results in the initial shift schedule with solution identifiers and their solution preparation times assigned to their respective shifts 2910.

FIG. 31 is an example of an initial shift schedule for solution preparation vessel 101. Exemplary solution identifiers are shown in column 3102. Column 3102 illustrates exemplary solution identifiers for the solutions used in the biopharmaceutical production process. Solution identifiers 3102 with date entries in corresponding An exemplary value for hours per solution prep shift is given in box 2804. Exemplary values for number of days per preparation cycle is given in column 1610. Exemplary values of solution prep dates of each solution is given in column 2906.

FIG. 30 further illustrates step 1318, back scheduling solution preparation in the initial shift schedule. Solution preparation is initially scheduled in steps 1302-1316 without considering the possibility of scheduling conflict. Back scheduling solution preparation is done in order to avoid conflicts in the solution preparation process. Scheduling conflicts result from scheduling more solution preparation cycles for a solution preparation vessel than can be accommodated in the amount of time available. For example, a scheduling conflict will occur if a particular solution preparation vessel is scheduled for twenty hours of solution preparation on one sixteen hour day. The present invention back schedules those solution preparation cycles that do not fit into their scheduled shift or day. For example, if a solution preparation vessel is scheduled for three solution preparation cycles of three hours each, the solution preparation vessel is scheduled for nine hours of preparation activity. If the production facility runs on an eight hour day, not all of the solutions can be prepared as scheduled. The present invention back schedules one of the solution preparation cycles, leaving six hours of solution preparation to be completed in one day. The back scheduled solution preparation cycle is rescheduled to the first previous available

shift so that the solution is prepared in time for use in the biopharmaceutical production process as scheduled in the process time line. After step 1318 is completed, the solution preparation time line is in proper form for use as a solution preparation and scheduling and management tool.

Step 1318 begins at step 3002, successively summing the solution preparation times for
5 each of the days or shifts in the initial shift schedule 2910. the solution preparation times are summed in order to determine the total solution preparation time for each solution preparation vessel on each shift. For the purpose of summing the solution preparation times, a shift is the number of hours in one biopharmaceutical production process day (e.g., eight hours for a single shift plant, sixteen hours for a double shift plant, etc.). Step 2002 results in a list for each
10 solution preparation vessel of summed solution preparation times for each shift 3004. Summed solution preparation times 3004 are compared with the available shift hours/day 2804 in step 3006. If the sum of the scheduled solution preparation times 3004 exceeds the number of shift hours available 2804, solutions are marked as "back scheduled" and are rescheduled for the first previously available shift. From the previous example, one of the three hour solution preparation
15 cycles is to be rescheduled for the first previously available shift, leaving six hours of solution preparation in the eight hour shift. If the originally scheduled day for the nine hours of solution preparation was Wednesday, the three hour solution preparation would be back scheduled to Tuesday. After a solution that doesn't fit into the current day has been back scheduled, it is removed from the current day schedule.

20 If step 3006 determines that the number of shift hours 2804 available exceeds the sum of the scheduled solution preparation times 3004, step 3010 determines if any solution is scheduled for preparation on the current shift. If step 3010 determines that a solution is scheduled for preparation in the current shift, step 3012 leaves the solution scheduled for preparation in the shift schedule.

25 If step 3010 determines that no solutions are assigned to the solution preparation vessel for the shift that is being evaluated, step 1318 continues to step 3014. Step 3014 determines if any solutions have been back scheduled to the current shift for preparation for a later shift. If no solution preparation cycles have been back scheduled to the current shift, the process continues to step 3002 where the next shift is analyzed for back scheduling. If step 3014 determines that
30 solution preparation cycles have been back scheduled, the process continues at step 3016. Step

3016 checks the original scheduling date on the back scheduled solution preparation cycle to determine if the back scheduled date is earlier than the original scheduling date minus the periodicity of the back scheduled solution. For example, if the solution has been successively back scheduled for four days (i.e., the preparation cycle of the solution had to be scheduled back
5 four days in order to fit into a shift), and its periodicity was two days, the back scheduled prep would be potentially interfering the previously scheduled prep of the same solution thereby indicating a shift schedule capacity error.

If step 3016 determines that the solution is back scheduled beyond its periodicity, an alarm is raised indicating that a system capacity issue exists at step 3020. If step 3016 determines that
10 the back scheduled solution preparation cycle not earlier than its orbitally scheduled date minus its periodicity, the solution preparation cycle is scheduled for the current shift at step 3018.

FIG. 32 further illustrates step 1320, generating solution preparation schedule 3210. Solution preparation schedule 3210 schedules each task associated with solution preparation for the biopharmaceutical process based on the back-scheduled shift schedule 3202 and the solution
15 preparation procedure 3212. Solution preparation schedules 3210 are generated for each solution preparation vessel that has an assigned solution. Back-scheduled initial shift schedule 3202, as generated in Step 1318, contains the solution preparation vessel to solution preparation assignment for each of the shifts in the initial shift schedule 2910. Step 1320 is performed for each of the shifts in the initial shift schedule 2910, thereby scheduling all of the solution preparation tasks for
20 each solution preparation vessel on each shift.

Step 1320 begins at Step 3206, determining the number of solution preparation that are scheduled for the current shift in the back-scheduled initial shift schedule 3202. If no solutions are scheduled for preparation, step 1320 continues to step 3204 which moves to the next shift in the back-scheduled initial shift schedule 3202. If there are solution preparations scheduled for the
25 current shift, step 1320 continues to step 3208. Step 3208 generates the solution preparation schedule 3210 from the solution preparation procedure data 3212 for each solution preparation scheduled in the shift. For example, if two solutions are scheduled to be prepared in solution preparation vessel 101, each task in each solution preparation procedure is scheduled out in solution preparation schedule 3210. An exemplary solution preparation procedure 3212 is
30 illustrated in FIG. 14 (steps 1420, 1408, 1414, 1418, 1426, 1432, and 1436).

FIG. 15 illustrates exemplary solution preparation procedure data, as described above, used to generate solution preparation schedule 3210. Step 3208 schedules out each task for each solution preparation assigned to the current shift. After step 3208, and if there are additional shifts in the back-scheduled initial shift schedule 3202, step 1320 continues at step 3204
5 proceeding to the next shift in back-scheduled initial shift schedule 3202. Step 1320 repeats to schedule all of the solution preparations in the back-scheduled initial shift schedule. Step 1320 results in, therefore, solution preparation schedule 3210 which is a time line, by shift, for each solution preparation task for each solution preparation assigned to a solution preparation vessel.

3.0 Equipment Preparation Scheduling Module

10 The object of the equipment preparation module is to simulate, schedule and model equipment preparation and loading in the biopharmaceutical production process. Equipment used in the biopharmaceutical production becomes soiled and must be cleaned, wrapped and sterilized in order to be used again. The process of cleaning, wrapping and sterilizing is known as equipment preparation. A piece of equipment that has been used in the biopharmaceutical
15 production process and requires preparation before it can be used again is called a soiled process component. Equipment preparation is performed in order to sustain the biopharmaceutical production process.

Current methods for the design equipment preparation procedures typically fall short of accurately defining the relatively complex procedures that are executed in an equipment prep area.
20 As a result the equipment and work areas associated with equipment prep are usually inefficiently designed. Since the cleaning and sterilizing (prep) equipment associated with equipment prep activities are capital and utility intensive, an improved method for accurately modeling and optimizing these areas of a biopharmaceutical production facility is needed. The preferred embodiment provides a computer simulation method for the design and scheduling of equipment
25 prep operations which is more accurate and efficient than conventional design methods.

FIG. 33 is a flowchart illustrating an overview of the process for scheduling and simulating equipment preparation in a biopharmaceutical production process. Step 3302 generates a preparation equipment protocol table. A preparation equipment protocol is a protocol for the

operation of a piece of preparation equipment. Preparation equipment protocols usually include a plurality of equipment preparation tasks. A preparation task is a step in the equipment preparation process. For example, in a glassware dryer, a task may be loading the dryer, preheating the dryer, drying the glassware, unloading the dryer, etc. A preparation equipment
5 protocol table is a set of standard preparation equipment protocols to clean soiled process components. Preparation equipment protocols are usually developed through experimentation and quality assurance testing. The preparation equipment protocols that prepare the soiled process components for reuse most effectively and to the required levels of cleanliness become the preparation equipment protocols.

10 Preparation equipment protocols are associated with specific pieces of preparation equipment. Examples of preparation equipment are bench sinks, wash stations, glassware washers, glassware dryers, carboy washers, carboy dryers, autoclaves, steam sterilizers, etc. Furthermore, there may be multiple preparation equipment protocols per piece of preparation equipment. For example, there may be four preparation protocols associated with each type of
15 bench sink, each having different combinations of bench sink cleaning tasks and durations. Although the preferred embodiment describes a finite set of preparation equipment, soiled process components and preparation equipment protocols, one of ordinary skill could easily expand the process described herein to any preparation equipment or soiled process components.

Step 3304 generates an equipment preparation procedure table. An equipment preparation
20 procedure is a standard procedure comprising a plurality of preparation equipment protocols by which a soiled process component is cleaned and sterilized for reuse in the biopharmaceutical production process. For example, an equipment preparation procedure for a carboy may include the preparation equipment protocols of bench sink rinsing, bench sink cleaning, carboy washing, carboy drying, wrapping and sterilization in an autoclave. Different types of soiled process
25 components require different combinations of preparation equipment protocols in order to be readied for reuse in the biopharmaceutical production process, thereby defining different equipment preparation procedures. As with preparation equipment protocols, equipment preparation procedures are determined through experimentation, quality assurance and quality control. Each type of equipment used in the biopharmaceutical production process has an
30 associated equipment preparation procedure.

An equipment preparation procedure table is a list of preparation equipment protocols and their associated information that define an equipment preparation procedure for each of the soiled process component types. In a preferred embodiment, there are equipment preparation categories for each piece of soiled process components. Instead of an equipment preparation procedure associated with each type of soiled process component, there is a an equipment preparation procedure associated with each equipment preparation category. Preparation equipment protocols associated with each of the different equipment preparation categories are placed together in a table format to provide the preparation procedures for each piece of soiled process components assigned to an equipment preparation category.

Step 3306 generates the equipment dimension table. Equipment dimensions are the length, height and depth of a piece of process equipment requiring cleaning and sterilization (e.g., beaker, flask, carboy, stainless steel fittings, etc.). The equipment dimension table defines the dimensions of all process equipment potentially requiring cleaning after use in the biopharmaceutical production process. The equipment dimension table is determined directly from the list of equipment used in the biopharmaceutical production process. The equipment dimension list provides a means for determining the volume of the equipment to be cleaned in the biopharmaceutical production process, thereby allowing the calculation of the capacity of the preparation equipment.

Step 3308 generates a master list of equipment that may require preparation. Each unit operation in the biopharmaceutical production process is associated with preparation equipment. Step 3308 generates a master list of equipment associated with the biopharmaceutical production process and solution preparation process. In the preferred embodiment, the preparation equipment associated with each unit operation for both the biopharmaceutical production process and solution preparation process is defined when the unit operations for these activities are defined. As described above, the process equipment associated with unit operations of a biopharmaceutical production process are incorporated into a production process time line. Likewise the activities associated with each step of solution preparation is identified in step 1302 and incorporated into total solution preparation time for the solution preparation vessels 1428.

Step 3310 generates the equipment preparation load table. The equipment preparation load table includes data describing when particular soiled process components from the equipment

dimension table are available for preparation. For example, some information comes from the finish times for the tasks in process time line 906 that define when the soiled process components from the biopharmaceutical production process will be available for cleaning. Step 3310 generates the equipment preparation load table by comparing the process time line schedule with the
5 equipment preparation master list.

Step 3312 generates the equipment preparation load summary table. The equipment preparation load summary table is the sum of all equipment preparation load tables from each of the biopharmaceutical production processes active in the biopharmaceutical facility. For example, a facility may be producing multiple biopharmaceutical products in multiple processes. In such
10 a case, the preparation equipment handles equipment preparation for multiple biopharmaceutical production processes. Likewise, a facility may have multiple solution preparation suites. In such a case, the preparation equipment handles equipment preparation for multiple solution prep suites. Step 3312 generates the equipment preparation load summary table for the sum of all biopharmaceutical production processes by combining the equipment preparation load tables for
15 all of the biopharmaceutical production processes.

Step 3314 estimates the preparation equipment capacity. The capacity of the preparation equipment is determined in order to provide sufficient capacity to handle the load of soiled process components in the biopharmaceutical facility. Preparation capacity is the flow rate of soiled process components that the preparation equipment can accommodate. Preparation capacity is
20 estimated based on the flow rate of equipment from the preparation load summary table. The rate at which soiled process components are generated in the biopharmaceutical production facility is a good estimate of the capacity of the preparation equipment.

Step 3316 determines the equipment preparation time line. The equipment preparation time line includes scheduling each soiled process component through each piece of preparation
25 equipment in each of the equipment preparation procedures. Functional specifications for the preparation equipment and the utility load requirements for the preparation equipment can be generated from the equipment preparation time line. Functional specifications describe a piece of equipment with particularity. For example, functional specifications for a pump include pump type, flow rate, maximum and minimum input and output pressures, input and output fitting sizes,
30 electrical requirement, temperature range and type and frequency of required maintenance.

FIG. 34 further illustrates step 3302, generating the preparation equipment protocol table. Step 3302 begins with step 3404, generating the preparation equipment protocol identifiers 3408. Preparation equipment protocol identifiers 3408 are keys or codes which identify each preparation equipment protocol. Preparation equipment protocol identifiers 3408 allow each preparation equipment protocol to be identified in the equipment preparation module and are used to generate the preparation equipment protocol table. Step 3404 assigns unique preparation equipment identifiers 3408 to each of the preparation equipment protocols 3402. Preparation equipment protocol table 3402 also includes the task and duration information associated with each preparation equipment protocol. Next, step 3406 generates preparation equipment protocol table 3410. Preparation equipment protocol table 3410 is generated by assigning preparation equipment protocol identifiers 3408 to each preparation equipment protocol in preparation equipment protocol table 3402.

FIGS. 36A-36H are exemplary preparation equipment protocol tables 3410. Column 3408 in FIGS. 36A-36H illustrate exemplary preparation equipment protocol identifiers 3408. Preparation equipment protocol table 3410 contains information describing each preparation protocol. Preparation equipment protocol identifiers BS-1 through BS-5 identify individual bench sink preparation protocols. For example, FIG. 36A illustrates protocol task durations for the bench sink preparation equipment. Protocol task duration is the amount of time associated with a task in a preparation equipment protocol. For example, protocol BS-1 in FIG. 36A has a loading task duration of 5 minutes. Bench sink protocol BS-1, therefore, includes the step of loading the bench sink, which requires 5 minutes. Protocol task durations of prewash rinse with non-potable hot water (NPHW), prewash rinse with non-potable cold water (NPCW), detergent wash with reagent, post wash rinse with NPHW and NPCW, final rinse and hold dry are illustrated in FIG. 36A. Columns 3602 and 3604 are examples of protocol parameters. Protocol parameters are data elements that describe particular facets of a preparation equipment protocol. In the example of FIG. 36A, protocol parameters detergent wash reagent and grams of reagent per cubic foot are used to describe the detergent in the bench sink wash process.

FIG. 36B illustrates an exemplary preparation equipment protocol table for a wash station. Column 3408 of FIG. 36B illustrates exemplary preparation equipment protocol identifiers 3408 for a wash station. FIG. 36C illustrates an exemplary preparation equipment protocol table for

a glassware washer. Column 3408 in FIG. 36C illustrates exemplary preparation equipment protocol identifiers 3408 for a glassware washer. FIG. 36D illustrates an exemplary preparation equipment protocol table 3410 for a glassware dryer. Column 3408 in FIG. 36D illustrates exemplary preparation equipment protocol identifiers 3408 for a glassware dryer. FIG. 36D illustrates exemplary task durations for tasks associated with the glassware dryer protocols. Some examples of task durations are loading 3618, heat up 3620, drying 3624, cooling 3626 and unloading 3628, as shown by their respective columns. Column 3622 illustrates the drying temperature protocol parameter. FIG. 36E illustrates an exemplary preparation equipment protocol table 3410 for a carboy washer. FIG. 36F illustrates an exemplary preparation equipment protocol table 3410 for a carboy dryer.

FIG. 36G illustrates an exemplary preparation equipment protocol table for a steam sterilizer. Due to the multiple protocol parameters and task durations associated with steam sterilizer preparation equipment protocols, the preparation equipment protocol table of FIG. 36G is two-dimensional. Row 3608 illustrates exemplary preparation equipment protocol identifiers 3408 for the steam sterilizer. The steam sterilizer preparation equipment protocol table 3410 includes multiple protocol tasks 1-33 as illustrated in column 3606. Each of the tasks in the steam sterilizer protocol has associated protocol parameters and protocol durations as illustrated in columns 3608, 3610, 3612, 3614 and 3616. Row 32 in column 3606 of FIG. 36G illustrates exemplary values for the total time in minutes required for each of the different steam sterilizer protocols (protocol identifiers SS-1, SS-2 and SS-3). FIG. 36H illustrates an exemplary preparation equipment protocol table 3410 for a dry heat stabilizer.

FIG. 35 further illustrates step 3304 generating equipment preparation procedure table 3512. Equipment preparation procedure table 3512 includes data associated with each equipment preparation procedure, including the sequence of preparation equipment protocols and their individual durations as well as their cumulative duration over the entire procedure. Step 3304 begins at step 3506, generating equipment preparation procedure identifiers 3510. Equipment preparation procedure identifiers are tags or codes which identify equipment preparation procedures. FIGS. 37A and 37B illustrate an exemplary equipment preparation procedure table 3512. Row 3702 illustrates exemplary equipment preparation procedure identifiers 3510. EPC-1,

EPC-2, EPC-3, EPC-4, EPC-5, EPC-6 and EPC-7 are examples of codes which identify equipment preparation procedures.

Step 3508 generates equipment preparation procedure table 3512. Step 3508 generates equipment preparation procedure table 3512 from preparation equipment protocol tables 3502, equipment preparation procedures 3504 and equipment preparation procedure identifiers 3510. Equipment preparation procedures 3504 provides the list of preparation equipment protocols that identify a particular equipment preparation procedure and equipment assignment. FIG. 37A, for example, shows equipment preparation procedure EPC-1 includes (as shown in column EPC-1) preparation equipment protocols BS-1, BS-3, GD-1, and SS-1 in FIG. 37B. Equipment preparation procedures 3504 also include the equipment assignments for each of the equipment preparation procedures. Equipment assignments define the soiled process components associated with, or prepared by, each equipment preparation procedure. For example, a particular equipment preparation procedure may only be used to clean carboys. Step 3508 compares the preparation equipment protocols in the equipment preparation procedures 3504 with the preparation equipment protocol tables 3502. The protocol durations and protocol parameters provide the information in equipment preparation procedures table 3512. Equipment preparation procedure identifiers 3510 are assigned to each individual equipment preparation procedure in equipment preparation procedure table 3512.

FIGS. 37A and 37B illustrate exemplary equipment preparation procedure tables 3512. Row 3702 illustrates exemplary equipment preparation procedure identifiers EPC-1, EPC-2, EPC-3, EPC-4, EPC-5, EPC-6, and EPC-7. Equipment preparation procedure identifiers 3510 identify equipment preparation procedures for different categories of equipment. Exemplary equipment preparation procedure identifier EPC-5 includes the preparation equipment protocols of wash station (WS-1), carboy washer (CW-1), carboy dryer (CD-1), and steam sterilization autoclave 1 (SS-2). Associated with each of the preparation equipment protocols are task durations. Column 3704 illustrates task durations for equipment preparation procedure EPC-5. The task durations for each of the preparation equipment protocols are totaled to yield the equipment preparation procedure duration for EPC-5. Cumulative totals for the equipment preparation procedure duration are given in column 3706, rows 8, 15, 24, 31, 38, 45, 52, 66, 75 and 82. The

cumulative durations are the sum of all the previous preparation equipment protocol durations in the equipment preparation procedure.

FIG. 38 further illustrates step 3306, generating equipment dimension table 3816. Step 3306 begins at step 3806, generating the master equipment dimension list 3808. Step 3806 uses
5 the list of equipment requiring preparation 3802 and the equipment dimensions list 3804 to generate master equipment list 3806 which defines the dimensions of all process equipment that may cleaned by the equipment preparation procedure. List of equipment requiring preparation 3802 is a complete list of all the equipment used in the biopharmaceutical production process. List of equipment requiring preparation 3802 may be generated from the unit operations that
10 define the process time line 906 or solution preparation schedule. Alternatively, list of equipment requiring preparation 3802 may be provided by the system designer as the equipment used in the biopharmaceutical production process by design. List 3802 identifies those pieces of equipment that will need to be prepared in order to complete the biopharmaceutical production process. Equipment dimensions list 3804 is a master list of equipment dimensions for all of the equipment
15 available for use in the biopharmaceutical production process. Often, equipment dimensions list 3804 will be provided by the vender or manufacturer of the process equipment. List of equipment requiring preparation 3802 is compared to the equipment dimensions list 3804 in order to assign the equipment dimensions to the equipment used in the biopharmaceutical production process, resulting in master equipment dimension list 3808.

20 Next, step 3812 generates the equipment dimension table with segregated equipment preparation procedure identifiers. Step 3812 segregates the equipment dimension list into equipment preparation procedures as defined in the equipment preparation procedures and equipment assignment list 3504. The master equipment dimension list 3808 is segregated based on the equipment preparation procedure identifiers 3510 in order to generate equipment dimension
25 table 3816 according to equipment preparation procedure identifiers. The resultant equipment dimension table 3816 includes a list of specific process equipment and their associated equipment preparation procedure identifiers. Each particular equipment preparation procedure (e.g., EPC-1, EPC-2, EPC-3, etc.) is assigned to particular equipment types. Equipment dimension table 3816 also includes the dimensions of equipment to be prepared.

FIG. 39 illustrates an exemplary equipment dimension table 3816. Row 3902 illustrates exemplary equipment preparation procedure identifiers 3510. Rows 3904 identify the dimensions of each particular type of equipment involved in the equipment preparation process. Rows 3904 illustrates exemplary values for the dimensions of soiled process components to be cleaned in the equipment preparation procedure. Row 1 of rows 3904 illustrates exemplary values for the right-to-left dimension (R/L) in inches. Row 2 of rows 3904 illustrates exemplary values for the front-to-back dimension (F/B) in inches. Row 3 of rows 3904 illustrates exemplary values for top-to-bottom dimensions (T/B) in inches. Row 5 of rows 3904 illustrates exemplary values for volume in cubic inches (CI). Row 6 of rows 3904 illustrates exemplary values for volume in cubic feet (CF). CI and CF are computed directly from the rectilinear dimensional values in rows 1-3 of rows 3904.

Column 3906 illustrates exemplary dimensional values for siphon tube equipment in equipment preparation procedure EPC-1. Column 3908 illustrates exemplary dimensional values for instruments including pressure indicators (PI), optical density probe and pH probe. Column 3910 illustrates exemplary dimensional values for fittings including tees, elbows, crosses, reducers, hose barbs and clamps. Column 3912 illustrates exemplary dimensional values for small and medium plasticware. Column 3914 illustrates exemplary dimensional values for silicone and butyl rubber stoppers. Column 3916 illustrates exemplary dimensional values for small and large flexible tubing. Column 3918 illustrates exemplary dimensional values for small and medium glassware. Column 3920 illustrates exemplary dimensional values for one, twenty and forty-five liter polypropylene carboys. Column 3922 illustrates exemplary dimensional values for ten, twenty and forty-five liter borosilicate glass carboys.

FIG. 40 further illustrates step 3308, generating equipment preparation master list 4004. Equipment preparation master list 4004 includes the process equipment that may be soiled by unit operation tasks and the solution preparation procedure tasks in the biopharmaceutical production process. As described above, each task in unit operation master list 508 has associated process equipment. The process equipment associated with each unit operation task is added to the equipment preparation master list 4004 in step 4002. Step 4002 uses unit operation master list 508 to generate a master list of equipment that may require preparation after use in the biopharmaceutical production process. Each piece of equipment has an associated dimension as

defined in equipment dimension table 3816. Step 4002 compares unit operation master list 508 with equipment dimension table 3816 to assign the equipment dimensions to the equipment in unit operation master list 508 when generating equipment preparation master list 4004. Step 4002 compares solution preparation task list 4006 with equipment dimension table 3816 to assign the equipment dimensions to the solution preparation task list 4006 when generating equipment preparation master list 4004. After step 4002, equipment preparation master list 4004 contains the list of process equipment used in the biopharmaceutical production process that may become soiled process components requiring cleaning by the equipment preparation procedures.

FIG. 41 further illustrates step 3310, generating equipment preparation load table 4104.

Equipment preparation load table 4104 includes data indicating when soiled process components from the equipment preparation master list 4004 will be available from the biopharmaceutical production process. Step 4102 generates equipment preparation load table 4104 by combining solution preparation schedule 3210 and process time line 906 with equipment preparation master list 4004. Cumulative flow of equipment out of the biopharmaceutical production process as represented by solution preparation schedule 3210 and process time line 906 is compared with equipment preparation master list 4004 in order to provide the equipment dimensional information in equipment preparation load table 4104. Equipment preparation load table 4104 includes soiled process components, the schedule for when the soiled process components are available for equipment preparation procedures, the dimensional information associated with each soiled process component and which task in the biopharmaceutical production process or solution preparation process generated the soiled process components. Equipment preparation load table 4104 represents the volumetric flow rate of equipment out of the biopharmaceutical production process that needs to be prepared for later use in order to sustain continuous biopharmaceutical production.

FIGS. 42A-42E illustrate an exemplary equipment preparation load table 4104. Column 4202 illustrates exemplary task titles. Task titles 4202 may originate from solution preparation procedure tasks or the titles of tasks in unit operations. Column 4204 illustrates exemplary task end times. The values in columns 4204 represent the date and time various soiled process components will be available for cleaning and preparation in equipment preparation procedures. Columns 4206-4216 of FIGS. 42A and 42B illustrate exemplary values for soiled process

components available for preparation in equipment preparation procedures. In each of the columns, each of the soiled process components contains the number and cubic footage with which it is associated. FIGS. 42C-42D illustrate additional tasks in the biopharmaceutical production process. As before, columns 4218-4228 of FIGS. 42C-42D illustrate exemplary values for soiled
5 process components available for preparation in equipment preparation procedures.

FIG. 43 further illustrates step 3312, generating equipment preparation load summary table 4304. Equipment preparation load table 4104 defines when soiled process components from the equipment preparation master list 4004 will be available from all biopharmaceutical production processes active in the biopharmaceutical facility. Because single equipment preparation facilities
10 may be shared across multiple biopharmaceutical production processes, the equipment load tables 4104 are combined to create equipment preparation load summary table 4304. Equipment preparation load summary table 4304 allows the scheduling and simulation of equipment preparation procedures for the entire biopharmaceutical production facility.

FIG. 44 further illustrates step 3314, determining the capacities of the preparation
15 equipment 4416. Step 3314 begins with step 4404, generating an initial equipment preparation schedule 4408. An initial equipment preparation schedule 4408 is generated for each equipment preparation procedure (EPC-1, EPC-2, EPC-3, etc.). As stated above, each equipment preparation procedure is associated with specific soiled process components. The initial equipment preparation schedule 4408 begins prior to the earliest date that soiled process
20 components are available, as provided by the equipment preparation load summary table 4304.

The initial equipment preparation schedule 4408 is an initial schedule for the arrival of soiled process components at each piece of preparation equipment. Since the duration of each task in each of the equipment preparation procedures is known, the time at which soiled process components arrive at various preparation equipment is calculated directly by adding the duration
25 of each task from the preparation equipment protocol table 3410 to the equipment preparation load summary table 4304. The time at which each soiled process component arrives at a particular step in a preparation equipment protocol is the sum of previous equipment preparation procedure tasks and the time which the soiled process component became available, as indicated in the equipment preparation load summary table 4304. Scheduling the soiled process components that arrive at

each piece of preparation equipment allows the peak loading on the preparation equipment to be determined. The peak loading of the preparation equipment can then be used to determine the size and capacity of the preparation equipment.

Step 4412 compares the peak cubic footage load, as determined in step 4410, with the cubic footage of the largest soiled process component from the equipment dimension table 3816. Step 4412 selects the larger of the peak cubic foot load and the cubic footage of the largest equipment item from the equipment dimension table.

Step 4414 uses the larger peak CF value as determined in step 4412 to generate the capacities for the preparation equipment 4416. Capacities for the preparation equipment 4416 will need to be high enough to handle the peak cubic footage of soiled process components that need to be prepared in the equipment preparation procedure. The capacities determined in step 4414 and stored in table 4416, therefore, are the maximum capacities for the preparation equipment. Once the necessary capacity for the preparation equipment has been determined, an equipment prep time line can be generated.

FIG. 46 further illustrates step 3316, generating the equipment preparation time lines 4610. Equipment preparation time lines 4610 include scheduling information for each soiled process component through each piece of preparation equipment in equipment preparation procedures. Equipment preparation time line 4610 includes the schedule of operation for each piece of preparation equipment. Equipment preparation time lines 4610 also include scheduling information for each particular facet of preparation equipment operation including resource loads for labor, utilities, disposables, reusables, maintenance, calibration, etc. Together with the capacity data determined in step 4414, equipment preparation time line 4610 allows the determination of functional specifications for preparation equipment to which cost and other data can be matched.

Step 3316 begins with step 4606, generating the final equipment preparation shift schedules for each piece of preparation equipment. As stated above, after the preparation equipment capacities have been determined in step 3314, the maximum load capacities for the preparation equipment 4602 are known. Capacities for preparation equipment 4416 define the maximum load capacities for preparation equipment 4602. Minimum load capacity for preparation equipment 4604 is a value set by the biopharmaceutical production process designer in order to maximize

efficiency or for the validation of equipment preparation procedure. For example, a biopharmaceutical production process designer may determine that sterilizer equipment should not be operated at less than fifty percent of its load capacity. The sterilizer equipment, therefore, would be operated only when sufficient volume of soiled process components have been accumulated. Step 4606 generates the final equipment preparation shift schedules for each piece of equipment based on the maximum load capacities for preparation equipment 4602, the minimum load capacities for preparation equipment 4604, and equipment preparation procedure table 3512. The final equipment preparation shift schedules include the load cycling through the preparation equipment dictated by the minimum load capacities 4604 and the maximum load capacities 4602. Maximum load capacities 4602 and minimum load capacities 4604 define when each particular protocol in the equipment preparation procedure table 3512 is executed. The final equipment preparation shift schedules contain accurate scheduling of the operation of each

Step 4608 generates the equipment preparation time lines 4610. The equipment preparation time lines 4608 differ from the final equipment preparation shift schedules, as determined in step 4606, by providing detailed scheduling of the tasks associated the prep equipment protocols in equipment prep procedure table 3512. Equipment preparation time lines 4610 are generated by comparing equipment preparation procedure table 3512 with the final equipment preparation shift schedules for each piece of preparation equipment. Equipment preparation time lines 4610 contain the time data for specific tasks and operation of preparation equipment.

FIG. 47 illustrates the process of generating preparation equipment functional specifications 4706. Preparation equipment functional specifications list 4706 contains functional specifications and costs associated with each piece of preparation equipment used in the equipment preparation procedure. Maximum load capacities for preparation equipment 4602 is used with equipment preparation time lines 4610 to provide the necessary specifications for the preparation equipment in the preparation equipment procedure. Step 4704 compares the specifications of maximum load capacities 4602 and equipment preparation time lines 4610 to determine which preparation equipment units from master equipment and cost list 4702 are required for the equipment preparation procedures. Master equipment and cost list 4702 contains the functional specifications of all of the available preparation equipment and their associated costs. Preparation

equipment is selected from master equipment and cost list 4702 based on functional specification matching with equipment preparation time lines 4610 and maximum load capacities for the preparation equipment 4602. The result of step 4704 is preparation equipment list with functional specifications and cost 4706, which is a subset of master equipment and cost list 4702.

- 5 Preparation equipment list with functional specifications and costs 4706 provides a means to more accurately match required preparation equipment with detailed cost and other data such as loads for utilities maintenance, calibration, quality assurance and quality control testing, etc.

FIG. 48 illustrates a process of generating preparation equipment utility time line 4810.

- The preparation equipment utility time line 4810 provides the utility requirements for the
10 equipment preparation process. The preparation equipment utility time line 4810 includes the utility requirements for each piece of preparation equipment and the associated date and time for the requirements. The preparation equipment utility time line 4810 allows the calculation of utility costs associated with each piece of preparation equipment and allows a biopharmaceutical facilities designer to determine the necessary utility supply to the preparation equipment. The
15 process of generating preparation equipment utility time line 4810 begins with step 4804, generating the preparation equipment utility table. The preparation equipment utility table includes a list of the preparation equipment functional specifications from preparation equipment list 4706 matched with the utility data for each piece of preparation equipment as given by preparation equipment utility data 4802. Preparation equipment utility data 4802 includes the
20 requirements for each piece preparation equipment during each task in a preparation equipment protocol. Examples of utility data are electrical power requirements, potable and nonpotable hot and cold water requirements, waste water requirements, steam requirements, etc. Step 4804 generates preparation equipment utility table 4806 by matching the data from equipment preparation equipment list 4706 with preparation equipment utility data 4802 on a preparation
25 equipment by preparation equipment basis.

- Step 4808 generates preparation equipment utility time line 4810. Step 4808 matches the data in preparation equipment utility table 4806 with equipment preparation time line 4610 to generate preparation equipment utility time line 4810. Preparation equipment utility time line 4810 schedules out the utility requirements for each piece of preparation equipment on a for each
30 task in the preparation equipment protocols. Each of the tasks in equipment preparation time line

4610 is matched to the data in preparation equipment utility table 4806. Based on equipment preparation time line 4610 and the utility requirements for each piece of preparation equipment as described in preparation equipment utility table 4806, the utility requirements for each of preparation equipment is scheduled out in preparation equipment utility time line 4810. The utility time line 4810 when combined with the utility time lines from other manufacturing operations such as biopharmaceutical production, solution preparation, etc. provides peak loading data for the accurate sizing of utilities. The detailed data of the equipment time lines allows for the identification and optimization of utility peak loads and cost through the analysis of well documented operations schedules.

10 4.0 *Equipment Preparation Refinement*

In an alternative embodiment of the present invention, peak loading, described above, may be refined. That is, a Peak Load Scheduling Frame (PLF) is defined for solution usage and used to optimize the use of three classes of custom installed process vessels for Batch Process Manufacturing: (1) Solution Prep Vessels (SPV) that are used to prepare solutions required in batch process manufacturing; (2) Pooled Solution Storage Vessels (PSSV) that are used to store large volume solutions required in batch process manufacturing in a central area and supply them to various use points via distribution manifolds; and (3) Portable Storage Vessels that are used to store small volume solutions required in batch process manufacturing and local to their use point.

In this embodiment the storage and distribution of a given solution formulation that is required in more than one use point at different locations in a Batch Process Facility (BPF), whether the multiple use points be in a single process and/or multiple processes within the same BPF, is addressed.

A PLF defines the start and duration of a reiterative scheduling frame in which an accurate profile of solution usage for a BPF is first observed once a the BPF has reached steady state. Once a PLF for a solution has been determined, the preferred embodiment provides a mechanism to accurately define how much Equipment Turnaround Times (ETT) is available for SPVs, PSSVs and PSVs relative to the scheduled use point requirements for the solutions that they support. Once the ETTs for these vessels has been determined their quantity can be optimized. SPVs and

PSSVs account for a significant part of the field installation costs for a batch process facility since this work is typically highly customized and therefore design and installation intensive. Therefore, a mechanism that can optimize the quantity and use of SPVs and PSSVs is of significant value to Batch Manufacturing Operations as they apply to the biopharmaceutical or
5 other batch process industries.

This embodiment is particularly useful for designing batch process facilities that accommodate multiple processes each of which is subdivided into multiple process stages. A Process Stage is a set of one or more process Unit Operations grouped together to facilitate Divergent and Convergent Process Flow Schemes. A Divergent Process Flow Scheme occurs
10 when the output from one the last Unit Operation in a Process stage is split to feed two or more concurrent downstream process stages. An example of a Divergent Process Flow Scheme is when the contents of the last seed bioreactor in a large scale mammalian cell process is split to seed two or more production bioreactors that will operate in parallel to each other to produce product for further purification. Such splitting of bioreactor capacity in a large-scale process is typically
15 practiced to limit the risk of product loss if a single reactor becomes contaminated and its contents need to be discarded. In addition, careful planning and scheduling of process stages in this and other instances can be used to reduce the size and optimize the use of process equipment, labor and utilities. A Convergent Process Flow Scheme occurs when the outputs from two or more upstream process stages are pooled for joint downstream processing. An example of a Convergent
20 Process Flow Scheme is when the harvests of two or more production bioreactors in the above Divergent Process Flow Scheme Example are pooled for joint purification.

Referring to FIG. 66, a block diagram 6600 illustrates the principles of Divergent and Convergent Process Flow Schemes described above. Many batch processes employ combinations of both Schemes as illustrated above. The three levels of design cycles previously discussed can
25 be applied to any combination of Divergent and Convergent Process Flow Schemes in a process.

Referring to FIG. 67, a high-level block diagram 6700 illustrates the Definition and Use of PLFs to determine the Quantity of PSSVs required for a Given Solution in a BPF. In Step 6702, the definition of a PLF for a given solution to accurately predict the usage profiles of a given solution over multiple use points in a BPF. FIG. 68 further illustrates the definition of the
30 PLF Duration (PLFD) associated with Step 6702 for a given solution. In Step 6802, the Batch

Cycle Offsets (BCO) for each process in the BPF are obtained from the client based on their process development information. Step 6804 illustrates the determination of PLFD based on the Lowest Common Multiple (LCM) of the above BCOs to provide the PLFD result in Step 6806. FIG. 69 further illustrates the determination of the start date/time for the PLF for a given solution in a BPF (PLFS). In Step 6902 an estimate of the Batch Cycle Duration (BCD) for each process in the BPF utilizing a given solution is obtained from the client based on their process development information. In Step 6904 the Number of Load Frames per BCD (NLF/BCD) for each process in the BPF utilizing a given solution is determined by dividing the BCD for each process by the PLFD of Step 6806. In Step 6906 the Peak Load Frame Number (PLFN) for a given solution is provided from the maximum NLF/BCD value for all the processes in the BPF utilizing that solution. In Step 6908 the PLF Start Date/Time (PLFS) is determined by adding the latest Process Start Time of the processes accommodated by the BPF to the product of the PLFN * the PLFD. The results of the procedures illustrated in FIGs. 68 and 69 provide both the Start Time and Duration (and hence the end time) of the PLF for a given solution in a BPF.

FIG. 70 provides an example of a table used to determine both the PLFD and PLFS for a list of solutions in a BPF. In Column 7002, a list of Solutions required by a BPF is illustrated. In Column 7004 the shelf life of each solution is illustrated. The shelf life of a solution is the number of days it can be stored before becoming unusable in a process and must be discarded. In Column section 7006, the BCO for each process (1-6) in the BPF is provided for each solution required by a respective process. In Column section 7008 the LCM for all the BCO for each process related to a given solution is calculated. The resulting LCM is provided in Column 7010. In Column Section 7012 the number of Load Frames for each Process is determined relative to each solution by dividing the BCD by the PLFD. The largest Load Frame Value for each solution is determined as its respective PLF number in Column 7014. The Latest Process Start Date is determined in Column Section 7016 for each process relevant to a given solution. In Column Section 7018 the PLFS is calculated by adding the product of the PLFD multiplied by the PLFN, to the Latest Process Start Date for each respective solution.

FIG. 71 illustrates a Material Consumption Table (MCT) used for quantifying the amount of reagents consumed per batch cycle of product. The MCT is an important tool for both quantifying reagent costs per batch, as well as summarizing the date/times that various solutions

are required by for their respective process streams within a Process Stage. The association of Process Solution formulations with specific process streams is defined in the Process Parameters Table for a Process. The quantities of each solution formulation required by respective process streams are determined by the Block Flow Diagram. The date/time that specific solutions are
5 required by their respective process streams is defined by the Process Time Line.

Row 7102 of the sample MCT lists a sequence of Unit Operations comprising a sample Process Stage. Row 7104 lists sample Process Stream Tags associated with a hypothetical Block Flow Diagram for each Unit Operation. Row 7106 lists the Solution Tags that define the Solution Formulations associated with each process stream as defined in the Process Parameters Table for
10 a process. Rows 7108-7112 summarize the design cycles associated with each unit operation and therefore each process stream as defined in the Unit Operations List for a process. Row 7114 lists the date/times that the respective solutions are required by the respective process streams, as defined by the Process Time Line for a sample process. Row 7116 lists the date/times that the respective solutions are completed use by the respective process stream, as defined by the Process
15 Time Line for a process. Row section 7118 lists the quantities of reagents consumed by respective process streams based on the volumes per process stream in Row 7126 (from Block Flow Diagram) and their respective formulations in Row 7106.

Row 7120 lists the cost of reagents consumed by each Unit Operations based on the volumes per process stream in Row 7140 and their respective formulations in Row 7106. Row
20 Section 7122 lists the quantities of USP Purified Water and Water For Injection (WFI) required per process stream, respectively. Row 7124 lists the volume of solution required per process stream per unit operation cycle. Row 7126 lists the volume of solution required per process stream per Cluster Cycle as calculated from Row 7124 times the number of Cluster Cycles from Row 7110. Row 7128 lists the volume of solution required per process stream per batch cycle
25 as calculated from the volume per Cluster Cycle in Row 7124 divided by the number of Batch Cycles per Process as defined in Row 7112. Row 7130 lists the flow rate required by each process stream as determined by in the calculation section of the Process Time Line.

The preferred embodiment for determining the ETT available for a PSSV employs the modulo of the respective start and finish date/times for each solution in its respective process
30 stream relative the PLFS and PLFD as a means of modeling the load profile for a respective

solution in the PLF. As will be apparent to one skilled in the mathematics and computer arts, the modulo operation returns the remainder after integer division of a first number by a second number. In the preferred embodiment, the modulo calculation has been used as a means of determining the Solution Usage Start Date/Time (SUS) for a Solution in a respective process stream relative to the PLFS, regardless of which Load Frame other than the PLF the date/time may originate from (before or after the PLF). In principle this determination is performed by subtracting the PLFS date/time from the SUS for a given solution in order to base line the given date relative to the start of the PLF. The modulo of the given date is then calculated by dividing it by the PLFD. The remainder of this division or modulo provides the time duration beyond the PLFS that the SUS would be when re-indexed from its Load Frame of origin to the PLF. Adding the PFLS to this modulo value provides the re-indexed SUS relative to the PLFS.

FIG. 72 further illustrates the use of the modulo function for the Determination of the Latest Solution Usage End Time for a given solution in the PLF as show in Step 6704 for a process stage. In the preferred embodiment, an array of SUSs is obtained from Row 7114 in the MCT. In Step 7202, the PLFS from Step 6910 is subtracted from each array value to baseline the modulo calculation relative to the PLFS. The modulo of the resulting array values is calculated using the PLFD from Step 6806 as the divisor resulting in an array of modulo values that reflect their respective SUS relative to the PLFS. The PLFS value is then added back to each modulo value in the said array resulting in an array of SUSs that have been re-indexed to their relative times in the PLF based on the PLFS. In Step 7204 the resulting array values are evaluated to see if any are less than zero. Array values less than zero indicate SUSs in the original array from Row 7114 that have a date that is earlier than the PLFS. To these array values the PLFD is added in Step 7206 in order to complete the re-indexing of all original array values to their relative times in the PLF. Array values that are greater than or equal to zero need no further adjustment, as they are already properly re-indexed to the PLF based on the modulo calculation in Step 7202 (Step 7208).

In Step 7210 the SUS array values from 7114 are subtracted from the Array of Solution Usage Finish Dates/Times (SUF Array) from Row 7116 in the MCT to yield an Array of the Solution Usage Duration (SUD Array) for each Process Stream in the given Process Stage. The values in the SUD are added to the values from Steps 7206 and 7208 to yield an array of Solution

Usage Finish Dates/Times that have been re-indexed to the PLF based on the re-indexed SUS values in Steps 7206 and 7208 (RSUF Array). In Step 7214, an array of Solution Tag Identifiers (STI Array) from Row 7114 in the MCT for the given Process Stage that corresponds to the values in the RSUF Array is evaluated to see if the respective STIs match the STIK from Step 5 7212. If the STI for a process stream corresponding to a RSUF Array value does not match the STIK, the respective RSUF Array value is omitted from further evaluation. If the STI for a process stream corresponding to a RSUF Array value does match the STIK it is further evaluated in Step 7218. In Step 7218, the RSUF Array values that have a corresponding STI Array value that matches the STIK are evaluated to find the largest RSUF value. The result of the evaluation 10 in Step 7218 (Step 7220) is the Latest Solution Usage End time in the PLF for the given solution in the given Process Stage (LSUF/ Process Stage). The LSUF/Process Stage value determined from each process stage in a BPF utilizing a given solution is stored for further evaluation as described below.

FIG. 73 further illustrates the Determination of Earliest Solution Usage Start Date/Time 15 (ESUS) in a PLF for a given solution from Step 6706. In the preferred embodiment, an array of SUSs is obtained from Row 7114 in the MCT. In Step 7302, the PLFS from Step 6810 is subtracted from each array value to baseline the modulo calculation relative to the PLFS. The modulo of the resulting array values is calculated using the PLFD from Step 6706 as the divisor resulting in an array of modulo values that reflect their respective SUS relative to the PLFS. The 20 PLFS value is then added back to each modulo value in the said array resulting in an array of SUSs that have been re-indexed to their relative times in the PLF based on the PLFS. In Step 7304, the resulting array values are evaluated to see if any are less than zero. Array values less than zero indicate SUSs in the original array from Row 7014 that have a date that is earlier than the PLFS. To these array values the PLFD is added in Step 7306 in order to complete the re-indexing of all original array values to their relative times in the PLF. Array values that are 25 greater than or equal to zero need no further adjustment, as they are already properly re-indexed to the PLF based on the modulo calculation in Step 7302 (Step 7308).

In Step 7310 an array of Solution Tag Identifiers (STI Array) from Row 7014 in the MCT for the given Process Stage that corresponds to the values in the Re-indexed Solution Usage Start 30 Date/Times (RSUS) arrays from Steps 7306 and 7308 is evaluated to see if the respective STIs

match the STIK from Step 7212. If the STI for a process stream corresponding to a RSUS Array value does not match the STIK, the respective RSUS Array value is omitted from further evaluation. If the STI for a process stream corresponding to a RSUS Array value does match the STIK it is further evaluated in Step 7314. In Step 7314 the RSUS Array values that have a
5 corresponding STI Array value that matches the STIK are evaluated to find the smallest RSUS value. The result of the evaluation in Step 7314 (Step 7316) is the Earliest Solution Usage Start Date/Time in the PLF for the given solution in the given Process Stage (ESUS/ Process Stage). The ESUS/Process Stage value determined from each process stage in a BPF utilizing a given solution is stored for further evaluation below.

10 FIG. 73 further illustrates the Determination of the Available ETT at the Beginning of a PLF for a Given Solution in a Process Stage as shown in Step 6708. In Step 7302 the PLFS value from Step 6910 is subtracted from the ESUS/Process Stage value from Step 7216 to determine the available ETT at the beginning of the PLF for a given solution in a given Process stage (ETTB). The resulting value is stored for further use (Step 7304).

15 FIG. 74 further illustrates the Determination of the Available ETT at the End of a PLF for a Given Solution in a Process Stage as shown in Step 6710. In Step 7402 the PLFS value from Step 6910 is added to the LSUF/Process Stage value from Step 7216 to determine the available ETT at the beginning of the PLF for a given solution in a given Process stage (ETTE). The resulting value is stored for further use (Step 7404).

20 FIG. 75 further illustrates the Determination of the Total ETT available in a PLF for a given solution in a given Process Stage as shown in Step 6712. In Step 7502 the ETTB from Step 7304 is added to the ETTE in step 7404 to determine the Total ETT for a given solution in a given process stage (ETTS). The resulting value is stored for further use (Step 7504).

FIG. 76 further illustrates the Determination of the Total ETT available in a PLF for a given
25 solution in a given Process Stage as shown in Step 6712. In Step 7602, the ETTB from Step 7404 is added to the ETTE in step 7504 to determine the Total ETT for a given solution in a given process stage (ETTS). The resulting value is stored for further use (Step 7604).

If there is only one process stage in a BPF being evaluated for a given process solution then the ETTS from 7604 is evaluated in Step 6714 to see if it greater than the sum of the time required
30 to prepare the PSSV for recharging and the time to recharge the vessel. The time required to prepare

the vessel may involve the time to clean and/or sterilize the vessel. The vessel preparation time can be determined from a required vessel preparation procedure as defined by the user. The vessel recharge time is determined from the volume to be charged divided by the time period in which the vessel charging is to take place. If the ETTS is greater than the sum of the vessel preparation time and recharge time then a single storage vessel can be used to supply the demand of all the use points in a BPF for a given solution based on their schedule requirements in the PLF.

If the ETTS is less than the sum of the vessel preparation time and recharge time then more than one storage vessel will be required to supply the demand of all the use points in a BPF for a given solution based on their schedule requirements in the PLF. The latter case can be accommodated by either segregating use points for a given solution to different storage vessels or by having a backup storage vessel that can be prepared and recharged while another vessel is servicing all the use points for a given solution. This latter case can be met through either a "Dual Alternating Feed" (DAF) system where two storage vessels share a distribution system to all the use points for a given solution such that one storage vessel is "on line" while the other is being prepared and recharged. An alternative to the DAF system is a "Hold/Feed" system. In a Hold/Feed system a Feed Storage Vessel is continually on-line, supplying the use points for a given solution and is kept supplied periodically by a Hold Tank that is in turn prepared and recharged in a manner that it can keep the Feed Vessel continuously on line. In the Hold/Feed alternative the Feed Storage Vessel is kept on line as long as required by the demand of the use points it supplies.

In cases where there are multiple process stages in a BPF to be evaluated in order to determine an ETT for a given solution, a higher level evaluation must be performed of the collective LSUF and ESUS values from the respective individual process stages to determine their collective effect on the respective ETT. FIG. 77 illustrates the Determination of the Latest Solution Usage Finish Date/Time in a Peak Load Frame for a Given Solution in a BPF as derived from the ESUS values from Multiple Process Stages. In the preferred embodiment, an array of ESUS values obtained in Step 7316 from each process stage in the BPF requiring a given solution. In Step 7702, the PLFS from Step 6910 is subtracted from each ESUS Array value to baseline the modulo calculation relative to the PLFS. The modulo of the resulting array values is calculated using the PLFD from Step 6806 as the divisor resulting in an array of modulo values that reflect their respective ESUS values relative to the PLFS. The PLFS value is then added back to each modulo

value in the array, resulting in an array of ESUSs that have been re-indexed to their relative times in the PLF based on the PLFS (RESUS).

In Step 7704 the resulting RESUS values are evaluated to see if any are less than zero. Array RESUS values less than zero indicate ESUSs in the original array that have a date that is earlier than the PLFS. To these array values the PLFD is added in Step 7706 in order to complete the re-indexing of all original array values to their relative times in the PLF (FRESUS). Array values that are greater than or equal to zero need no further adjustment, as they are already properly re-indexed to the PLF based on the modulo calculation in Step 7702 (Step 7708).

In Step 7710 the ESUS Array values from 7316 are subtracted from an Array created from the LSUF values obtained from each process stage in the BPF (Step 7220). The result is an Array of the Solution Usage Duration for each Process Stage in the BPF (SUDS Array). The values in the SUDS Array are added to the values from the Steps 7706 and 7708 to yield an array of LSUF values that have been re-indexed to the PLF based on the re-indexed ESUS values in Steps 7706 and 7708 (RLSUF Array). In Step 7712 the RLSUF Array values are evaluated to find the largest RLSUF value. The result of the evaluation in Step 7712 is the Latest LSUF in the PLF for the given solution in the entire BPF (LLSUF). The resulting LLSUF value is stored step 7714 for further evaluation below.

FIG. 78 illustrates the determination of the earliest solution usage start date in the peak load frame for a given solution in a BPF as derived from the ESUS values from Multiple Process Stages. In the preferred embodiment, an array of FRESUS values created using the same procedure as defined in FIG. 77. In Step 7810, the FRESUS Array values are evaluated to find the smallest value. The result of the evaluation in Step 7812 is the Earliest FRESUS value in the PLF for the given solution in the entire BPF (EESUS). The resulting EESUS value is stored step 7812 for further evaluation below.

FIG. 79 further illustrates the determination of the available ETT at the beginning of a PLF for given solution in a BPF. In Step 7902, the PLFS value from Step 6910 is subtracted from the EESUS value from Step 7812 to determine the available ETT at the beginning of the PLF for a given solution in the BPF (PETTB). The resulting value is stored in Step 7904 for further use.

FIG. 80 further illustrates the determination of the available ETT at the end of a PLF for a given solution in a BPF. In Step 8002, the LLSUF value from Step 7714 is subtracted from the sum

of the PLFS value from Step 6910 and the PLFD from Step 6806 to determine the available ETT at the beginning of the PLF for a given solution in the BPF (PETTE). The resulting value is stored in Step 8004 for further use.

FIG. 81 further illustrates the determination of the Total ETT available in a PLF for a given solution in a given Process Stage. In Step 8102, the PETTB from Step 7404 is added to the PETTE in step 7504 to determine the Total ETT for a given solution in a given process stage (ETTP). The resulting value is stored for further use (Step 8104).

The ETTP from Step 8104 can be used to evaluate the need for storage vessel redundancy for a given solution in a BPF in the same manner that the ETTS from Step 7604 was used above to evaluate vessel redundancy for a given vessel for a Process Stage. The options for vessel redundancy when the Equipment Turn Around Time (ETTS or ETTP) is less than storage vessel prep and recharge time is the same in each instance.

5.0 Equipment Maintenance Scheduling Module

Equipment maintenance in a biopharmaceutical production facility is necessary to sustain the biopharmaceutical production process. The types and frequency of maintenance required is a function of the particular equipment used in the facility, as well as the frequency and nature of use. The equipment involved in the production process, solution preparation process, and equipment preparation all require regular maintenance during sustained operation. Often, maintenance frequency and cost are not considered in the design of a biopharmaceutical production facility. Maintenance costs, however, are a significant fraction of the cost of operating the biopharmaceutical facility and producing the biopharmaceutical product. Since maintenance is a significant cost of operating a biopharmaceutical production facility, a system and method for scheduling and modeling the maintenance of process equipment, solution preparation equipment and preparation equipment would allow the biopharmaceutical facility designer to predict and minimize the cost of maintenance. Additionally, scheduling and modeling maintenance of a biopharmaceutical production process would allow for more complete modeling of a biopharmaceutical production facility.

Modeling and scheduling biopharmaceutical production facility maintenance is based on the functional specifications and usage of the biopharmaceutical production process equipment. Each

piece of equipment has associated maintenance parameters. For example, a particular pump may require a new drive belt, seals and lubrication after a predetermined number of hours of operation. Filtration media in filters must be changed after a predetermined number of hours of use. Given equipment functional specifications, equipment maintenance requirements and production schedules
5 for biopharmaceutical production process equipment, equipment maintenance can be modeled and scheduled.

FIG. 49 illustrates the process of generating process equipment maintenance table 4906. Process equipment maintenance table 4906 includes maintenance procedures, maintenance duration (i.e., the amount of time required to perform the maintenance), reusables (i.e., those maintenance
10 items that must be replaced periodically), disposables (i.e., those maintenance items that must be replaced after every use), the maintenance period (i.e., the amount of use before the equipment must be serviced), and the number of hours required to complete the maintenance tasks for the equipment.

Step 4904 generates process equipment maintenance tables 4906 from the process equipment list and functional specifications 4908 and process equipment maintenance data 4902. Process
15 equipment list 4908 is generated from unit operation list 508. Unit operation list 508 includes the process equipment associated with each task in a unit operation. The process equipment list 4908, therefore, includes a list of process equipment from unit operation list 508. Process equipment list 4908 also includes functional specifications associated with each piece of process equipment in process equipment list 4908. Functional specifications describe a piece of equipment with
20 particularity. For example, functional specifications for a pump include pump type, flow rate, maximum and minimum input and output pressures, input and output fitting sizes, electrical requirement, temperature range and type and frequency of required maintenance.

Functional specifications associated with each piece of process equipment are determined from the block flow diagram 704, process time line 906 and equipment data sheets. Equipment data
25 sheets, usually vendor or manufacturer provided, are equipment specifications that provide the capacity and functional specifications for equipment available for use in the biopharmaceutical production processes. Each unit operation has associated process equipment. The functional specifications of the equipment, however, are rate- and time-dependent. Block flow diagram 704 defines the volume of solution and biopharmaceutical product handled by each unit operation. The
30 process time line 906 defines the rate at which solutions and biopharmaceutical product are handled

in each unit operation. The volume and rate information from the block flow diagram and process time line, therefore, define the operational parameters of the process equipment. The functional specifications of the process equipment are determined directly by matching the volume and rate parameters for the equipment with the volume and rate parameters in equipment data sheets. The functional specifications of the equipment from the equipment data sheet are then added to the process equipment list to form process equipment list with functional specifications 4908.

Step 4904 generates process equipment maintenance table 4906 from process equipment list with functional specifications 4908 and process equipment maintenance data 4902. Process equipment maintenance data 4902 includes functional specifications for each piece of process equipment and their associated maintenance information. Process equipment maintenance data 4902 includes replaceables, reusables, labor, cycle life and the cost of the associated maintenance item. Some examples of replaceables and reusables are: filters, gaskets, bearings, seals, belts, crank-shafts, lubricants and thermal media. Associated with each maintenance item is the number and identifier for the item, the quantity, the cycle life (i.e., the amount of time or use before replacement), and the cost per cycle. Also included in process equipment maintenance data 4902 is the amount of labor associated with each maintenance item and the number of dollars per cycle for the labor.

Step 4904 matches process equipment list with functional specifications 4908 with process equipment maintenance data 4902, to generate process equipment maintenance table 4906. Process equipment list with functional specifications 4908 is matched with process equipment maintenance data 4902 based on a comparison of functional specifications in the process equipment list 4908 and the process equipment maintenance data 4902. Step 4904 copies the process equipment maintenance data 4902 for each piece of process equipment in the process equipment list 4908, thereby creating process equipment maintenance table 4906.

FIGS. 64A-64AB illustrate an exemplary process equipment maintenance table 4906. Column 6402 illustrates exemplary unit operations and their associated process equipment, as determined from process equipment list 4908. FIGS. 64A-64E illustrate the process equipment maintenance data for unit operations 1-6, as illustrated in column 6402.

Column 6404 of FIG. 64A illustrates exemplary maintenance data values for the filter maintenance items. Included in column 6404 are item number, quantity, cycle life of the filter materials, unit cost of the filter materials, dollars per cycle of the filter material, the labor of hours

required to service the filter media, and the dollars per cycle for the labor. Item number identifies the stock number or part number of the item used in the maintenance procedure. Cycle life of the materials identifies the useful life the maintenance item. Quantity identifies the quantity of the maintenance item used in the maintenance procedure. Unit cost is the per unit cost of the maintenance item. Dollars per cycle is the quotient of the cost of the maintenance items and the cycle life of the maintenance items.

Column 6406 illustrates exemplary maintenance data for gasket maintenance items. Column 6408 of FIGS. 64A and 64B illustrates exemplary maintenance data for bearing maintenance items. Column 6410 of FIG. 64B illustrates exemplary maintenance data for seal maintenance items. Column 6412 of FIGS. 64B and 64D illustrate exemplary maintenance data for belt maintenance items. Column 6416 of FIG. 64C illustrates exemplary maintenance data for crank shaft maintenance items. Column 6418 of FIGS. 64C and 64D illustrates exemplary maintenance data for lubricant maintenance items. Column 6420 of FIG. 64D illustrates exemplary maintenance data for thermal media maintenance items. FIGS. 64E-64AB illustrate the same maintenance items as described in column 6404-6420, as associated with unit operations 7-22.

FIG. 50 illustrates the process of generating the process equipment maintenance time line 5004. Process equipment maintenance time line 5004 is a schedule maintenance items or procedures for process equipment in the biopharmaceutical production process. Step 5002 generates process equipment maintenance time line 5004 by applying the equipment scheduling data from the process equipment time line 906 data to the process equipment maintenance table 4906. Step 5002 calculates the accumulated usage time for each piece of equipment and schedules maintenance on the equipment at the times specified by the process equipment maintenance table 4906. Process equipment maintenance time line 5004 includes process equipment maintenance data from process maintenance data 4906 and the specific time and date when each piece of process equipment should be serviced. Step 5002, therefore, determines the number of unit operations or process cycles required to attain the cycle life rating on the maintenance item in order to trigger the maintenance processes.

FIG. 51 illustrates the process of generating solution preparation equipment maintenance table 5106. Solution preparation equipment maintenance table 5106 includes maintenance procedures, maintenance duration (i.e., the amount of time required to perform the maintenance),

reusables (i.e., those maintenance items that must be replaced periodically), disposables (i.e., those maintenance items that must be replaced after every use), the maintenance period (i.e., the amount of use before the equipment must be serviced), and the number of hours required to complete the maintenance tasks for the equipment.

5 Step 5104 generates solution preparation equipment maintenance table 5106 from the solution preparation equipment list and functional specifications 5108 and solution preparation equipment maintenance data 5102. Solution preparation equipment list 5108 is generated from preparation vessel identifier and associated volume list 1402. Preparation vessel identifier and associated volume list 1402 includes the solution preparation equipment associated with each
10 solution preparation vessel. The solution preparation equipment list 5108, therefore, includes a list of solution preparation equipment from preparation vessel identifier and associated volume list 1402. Solution preparation equipment list 5108 also includes functional specifications associated with each piece of solution preparation equipment in solution preparation equipment list 4809. The functional specifications for each solution preparation vessel and its associated solution preparation equipment
15 are included in preparation vessel identifier and associated volume list 1402 when it is defined.

Step 5104 generates solution preparation equipment maintenance table 5106 from solution preparation equipment list with functional specifications 5108 and solution preparation equipment maintenance data 5102. Solution preparation equipment maintenance data 5102 includes functional specifications for each piece of solution preparation equipment and their associated maintenance
20 information. Solution preparation equipment maintenance data 5102 includes replaceables, reusables, labor, cycle life and the cost of the associated maintenance item. Some examples of replaceables and reusables are: filters, gaskets, bearings, seals, belts, crank-shafts, lubricants and thermal media. Associated with each maintenance item is the number and identifier for the item, the quantity, the cycle life (i.e., the amount of time or use before replacement), and the cost per
25 cycle. Also included in solution preparation equipment maintenance data 5102 are the amount of labor associated with each maintenance item and the number of dollars per cycle for the labor.

Step 5104 matches solution preparation equipment list with functional specifications 5108 with solution preparation equipment maintenance data 5102, to generate solution preparation equipment maintenance table 5106. Solution preparation equipment list with functional
30 specifications 5108 is matched with solution preparation equipment maintenance data 5102 based

on a comparison of functional specifications in the solution preparation equipment list 5108 and the solution preparation equipment maintenance data 5102. Step 5104 copies the solution preparation equipment maintenance data 5102 for each piece of solution preparation equipment in the solution preparation equipment list 5108, thereby creating solution preparation equipment maintenance table 5106.

FIG. 52 illustrates the process of generating the solution preparation equipment maintenance time line 5204. Solution preparation equipment maintenance time line 5204 is a schedule maintenance items or procedures for solution preparation equipment in the biopharmaceutical production process. Step 5202 generates process equipment maintenance time line 5204 by applying the equipment scheduling data from the solution preparation equipment time line 3210 data to the solution preparation equipment maintenance table 5106. Step 5202 calculates the accumulated usage time for each piece of equipment and schedules maintenance on the equipment at the times specified by the solution preparation equipment maintenance table 5106. Solution preparation equipment maintenance time line 5204 includes solution preparation equipment maintenance data from process maintenance data 5106 and the specific time and date when each piece of solution preparation equipment should be serviced. Step 5202, therefore, determines the number of unit operations or process cycles required to attain the cycle life rating on the maintenance item in order to trigger the maintenance processes.

FIG. 53 illustrates the process of generating preparation equipment maintenance table 5306. Preparation equipment maintenance table 5306 includes maintenance procedures, maintenance duration (i.e., the amount of time required to perform the maintenance), reusables (i.e., those maintenance items that must be replaced periodically), disposables (i.e., those maintenance items that must be replaced after every use), the maintenance period (i.e., the amount of use before the equipment must be serviced), and the number of hours required to complete the maintenance tasks for the equipment.

Step 5304 generates preparation equipment maintenance table 5306 from preparation equipment list with functional specifications 4706 and preparation equipment maintenance data 5302. Preparation equipment list 4706 also includes functional specifications associated with each piece of preparation equipment as determined in step 3314. Preparation equipment maintenance data 5302 includes functional specifications for each piece of preparation equipment and their associated

maintenance information. Preparation equipment maintenance data 5302 includes replaceables, reusables, labor, cycle life and the cost of the associated maintenance item.

Step 5304 matches preparation equipment list with functional specifications 4706 with preparation equipment maintenance data 5302, to generate preparation equipment maintenance table

- 5 5306. Preparation equipment list with functional specifications 4706 is matched with preparation equipment maintenance data 5302 based on a comparison of functional specifications in the preparation equipment list 4706 and the preparation equipment maintenance data 5302. Step 5304 copies the preparation equipment maintenance data 5302 for each piece of preparation equipment in the preparation equipment list 4706, thereby creating preparation equipment maintenance table
- 10 5306.

- FIG. 54 illustrates the process of generating the preparation equipment maintenance time line 5404. Preparation equipment maintenance time line 5404 is a schedule maintenance items or procedures for preparation equipment in the biopharmaceutical production process. Step 5402 generates process equipment maintenance time line 5404 by applying the equipment scheduling data
- 15 from the preparation equipment time line 4610 data to the preparation equipment maintenance table 5306. Step 5402 calculates the accumulated usage time for each piece of equipment and schedules maintenance on the equipment at the times specified by the preparation equipment maintenance table 5306. Preparation equipment maintenance time line 5404 includes preparation equipment maintenance data from process maintenance data 5306 and the specific time and date when each
- 20 piece of preparation equipment should be serviced. Step 5402, therefore, determines the number of unit operations or process cycles required to attain the cycle life rating on the maintenance item in order to trigger the maintenance processes.

6.0 Equipment Calibration Module

- Equipment calibration in a biopharmaceutical production facility is necessary to sustain the
- 25 biopharmaceutical production process. Equipment calibration is essential to the accurate measurement and control of all key manufacturing operations. Instruments such as pressure indicators, temperature indicators, flow meters, load cells etc. are at the core of most manufacturing systems. The reliability of these instruments and the processes they serve is dependent on punctual

and consistent calibration programs. The types and frequency of calibration required is a function of the particular equipment used in the facility, as well as the frequency and nature of use. The equipment involved in the production process, solution preparation process and equipment preparation all require regular calibration during sustained operation. Often, calibration frequency and cost are not considered in the design of a biopharmaceutical production facility. Calibration costs and scheduling, however, are a significant fraction of the cost of operating the biopharmaceutical facility and producing the biopharmaceutical product. Since calibration is a significant cost of operating a biopharmaceutical production facility, a system and method for scheduling and modeling the calibration of process equipment, solution preparation equipment and preparation equipment would allow the biopharmaceutical facility designer to predict and minimize the cost of equipment calibration. Additionally, scheduling and modeling equipment calibration of a biopharmaceutical production process would allow for more reliable calibration programs to insure the adequate and consistent performance of all manufacturing systems. .

Modeling and scheduling biopharmaceutical production equipment calibration is based on the functional specifications and usage of the biopharmaceutical production process equipment. Each piece of equipment has associated calibration points. These calibration points typically include pressure indicators and transmitters, temperature indicators and transmitters, level sensors, flow meters, etc. All of these calibration points are required for the reliable operation of these process systems. Given equipment functional specifications, equipment calibration requirements and production schedules for biopharmaceutical production process equipment, equipment calibration can be modeled and scheduled.

FIG. 55 illustrates the process of generating process equipment calibration table 5506. Process equipment calibration table 5506 includes calibration procedures, calibration duration (i.e., the amount of time required to perform the calibration), the calibration period (i.e., the amount of use before the equipment must be serviced), and the number of hours required to complete the calibration tasks for the equipment.

Step 5504 generates process equipment calibration table 5506 from process equipment list with functional specifications 4908 and process equipment calibration data 5502. Process equipment calibration data 5502 includes functional specifications for each piece of process equipment and their associated calibration information. Process equipment calibration data 5502 includes replaceables,

reusables, labor, cycle life and the cost of the associated calibration item. As mentioned above, some examples of replaceables and reusables are: filters, gaskets, bearings, seals, belts, crank-shafts, lubricants and thermal media. Associated with each calibration item is the number and identifier for the item, the quantity, the cycle life (i.e., the amount of time or use before replacement), and the cost per cycle. Also included in process equipment calibration data 5502 are the amount of labor associated with each calibration item and the number of dollars per cycle for the labor.

Step 5504 matches process equipment list with functional specifications 4908 with process equipment calibration data 5502, to generate process equipment calibration table 5506. Process equipment list with functional specifications 4908 is matched with process equipment calibration data 5502 based on a comparison of functional specifications in the process equipment list 4908 and the process equipment calibration data 5502. Step 5504 copies the process equipment calibration data 5502 for each piece of process equipment in the process equipment list 4908, thereby creating process equipment calibration table 5506.

FIG. 56 illustrates the process of generating the process equipment calibration time line 5604. Process equipment calibration time line 5604 is a schedule calibration items or procedures for process equipment in the biopharmaceutical production process. Step 5602 generates process equipment calibration time line 5604 by applying the equipment scheduling data from the process equipment time line 906 data to the process equipment calibration table 5566. Step 5602 calculates the accumulated usage time for each piece of equipment and schedules calibration on the equipment at the times specified by the process equipment calibration table 5566. Process equipment calibration time line 5604 includes process equipment calibration data from process calibration data 5566 and the specific time and date when each piece of process equipment should be serviced. Step 5602, therefore, determines the number of unit operations or process cycles required to attain the cycle life rating on the calibration item in order to trigger the calibration processes.

FIG. 57 illustrates the process of generating solution preparation equipment calibration table 5706. Solution preparation equipment calibration table 5706 includes calibration procedures, calibration duration (i.e., the amount of time required to perform the calibration), reusables (i.e., those calibration items that must be replaced periodically), disposables (i.e., those calibration items that must be replaced after every use), the calibration period (i.e., the amount of use before the

equipment must be serviced)), and the number of hours required to complete the calibration tasks for the equipment.

Step 5704 generates solution preparation equipment calibration table 5706 from the solution preparation equipment list and functional specifications 5108 and solution preparation equipment calibration data 5702. Solution preparation equipment list 5108 is generated from preparation vessel identifier and associated volume list 1402. Preparation vessel identifier and associated volume list 1402 includes the solution preparation equipment associated with each solution preparation vessel. The solution preparation equipment list 5108, therefore, includes a list of solution preparation equipment from preparation vessel identifier and associated volume list 1402. Solution preparation equipment list 5108 also includes functional specifications associated with each piece of solution preparation equipment in solution preparation equipment list 4809. The functional specifications for each solution preparation vessel and its associated solution preparation equipment are included in preparation vessel identifier and associated volume list 1402 when it is defined.

Step 5704 generates solution preparation equipment calibration table 5706 from solution preparation equipment list with functional specifications 5108 and solution preparation equipment calibration data 5702. Solution preparation equipment calibration data 5702 includes functional specifications for each piece of solution preparation equipment and their associated calibration data.

Step 5704 matches solution preparation equipment list and functional specifications 5108 with solution preparation equipment calibration data 5702 to generate solution preparation equipment calibration table 5706. Solution preparation equipment list with functional specifications 5108 is matched with solution preparation equipment calibration data 5702 based on a comparison of functional specifications in the solution preparation equipment list 5108 and the solution preparation equipment calibration data 5702. Step 5704 copies the solution preparation equipment calibration data 5702 for each piece of solution preparation equipment in the solution preparation equipment list 5108, thereby creating solution preparation equipment calibration table 5706.

FIG. 58 illustrates the process of generating the solution preparation equipment calibration time line 5804. Solution preparation equipment calibration time line 5804 is a schedule of calibration items and procedures for solution preparation equipment in the biopharmaceutical production process. Step 5802 generates process equipment calibration time line 5804 by applying the equipment scheduling data from the solution preparation equipment time line 3210 data to the

solution preparation equipment calibration table 5706. Step 5802 calculates the accumulated usage time for each piece of equipment and schedules re-calibration on the equipment at the times specified by the solution preparation equipment calibration table 5706. Solution preparation equipment calibration time line 5804 includes solution preparation equipment calibration data from process calibration data 5706 and the specific time and date when each piece of solution preparation equipment should be calibrated. Step 5802, therefore, determines the number of unit operations or process cycles required to attain the cycle life rating on the calibration of the equipment in order to trigger re-calibration of the equipment.

FIG. 59 illustrates the process of generating preparation equipment calibration table 5906.

- 10 Preparation equipment calibration table 5906 includes calibration procedures, calibration duration (i.e., the amount of time required to perform the calibration), the calibration period (i.e., the amount of use before the equipment must be serviced), and the number of hours required to complete the calibration tasks for the equipment.

- Step 5904 generates preparation equipment calibration table 5906 from preparation equipment list with functional specifications 4706 and preparation equipment calibration data 5902. Preparation equipment list 4706 also includes functional specifications associated with each piece of preparation equipment as determined in step 3314. Preparation equipment calibration data 5902 includes functional specifications for each piece of preparation equipment and their associated calibration data. Preparation equipment calibration data 5902 includes labor, and cycle life of the associated with calibration.

- Step 5904 matches preparation equipment list and functional specifications 4706 with preparation equipment calibration data 5902, to generate preparation equipment calibration table 5906. Preparation equipment list with functional specifications 4706 is matched with preparation equipment calibration data 5902 based on a comparison of functional specifications in the preparation equipment list 4706 and the preparation equipment calibration data 5902. Step 5904 copies the preparation equipment calibration data 5902 for each piece of preparation equipment in the preparation equipment list 4706, thereby creating preparation equipment calibration table 5906.

FIG. 60 illustrates the process of generating the preparation equipment calibration time line 6004. Preparation equipment calibration time line 6004 is a calibration schedule calibration for

preparation equipment in the biopharmaceutical production process. Step 6002 generates process equipment calibration time line 6004 by applying the equipment scheduling data from the preparation equipment time line 4610 data to the preparation equipment calibration table 5906. Step 6002 calculates the accumulated usage time for each piece of equipment and schedules calibration on the equipment at the times specified by the preparation equipment calibration table 5906. Preparation equipment calibration time line 6004 includes preparation equipment calibration data from process calibration data 5906 and the specific time and date when each piece of preparation equipment should be calibrated. Step 6002, therefore, determines the number of unit operations or process cycles required to attain the cycle life rating on the calibration item in order to trigger the calibration processes.

7.0 *Quality Control Module*

Quality control in a biopharmaceutical production facility is necessary to ensure the safety and quality of the biopharmaceutical product. Quality control sampling and testing, at various points in the biopharmaceutical production process ensures contamination-free product during the process, solution preparation and equipment preparation. The type and frequency of quality control sampling and testing required in a biopharmaceutical production process is a function of the particular equipment used in the process, the frequency and nature of the equipment use and the particular step or task in which the equipment is engaged. Often, quality control testing, frequency and cost are not planned prior to the design of a biopharmaceutical production facility. Quality control, sampling and testing, however, play a significant role in scheduling the operation of a biopharmaceutical facility. Modeling and scheduling quality control sampling and testing in a biopharmaceutical production facility is based on the definitions of the basic steps in the biopharmaceutical production process. Quality control testing and sampling steps are specified for the production process, the solution preparation process and equipment preparation protocols.

FIG. 61 illustrates the process for generating a master quality control protocol table 6110. Quality control protocols are assays and testing procedures associated with quality control sampling and testing. Quality control protocols 6102 are defined by the biopharmaceutical facility designer, determined through testing and experimentation or specified by the vendor of the equipment in the

biopharmaceutical facility. Quality control protocols 6102 include quality control protocol parameters. Quality control parameters are values that define the quality control assays. Examples of quality control parameters are the category and title of the assay, the setup time for the assay, the time required to draw each sample, the time required to clean up after taking the sample(s) and the disposal material necessary to dispose of the samples after testing.

Step 6104 generates quality control protocol identifiers 6108 for each of quality control protocols 6102. Quality control protocol identifiers 6108 are tags or codes that identify individual quality control protocols 6102. Step 6106 assigns quality control protocol identifiers 6108 to the quality control protocols 6102 resulting in master quality control protocol table 6110. Master quality control protocol table 6110 includes quality control protocols 6102 and a unique quality control identifier 6108 associated with each of quality control protocols 6102.

FIG. 21 illustrates an exemplary master quality control protocol table 6110. Column 2102 illustrates three exemplary categories of quality control protocols including environmental, analytical, and *in vitro* biological quality control protocols. Column 2104 illustrates exemplary quality control protocol identifiers 6108. Column 2106 illustrates exemplary values for quality control protocol parameters. More specifically, column 2106 illustrates quality control protocol parameters for the number of man-hours required to setup, draw each sample and cleanup the sampling operations associated with each quality control protocol. Setup and cleanup parameters define the amount of time necessary to setup prior to and cleanup after quality control protocol sampling. The per sample quality control protocol parameter defines the amount of time required to draw each sample. For example, 10 samples of temperature (quality control protocol identifier E-1) would require 0.5 man-hours to set up, 1.0 man-hours to sample ($0.1 \text{ hours/sample} \times 10 \text{ samples}$) and 0.5 man-hours to clean up.

FIG. 62 illustrates the process of generating master quality control sample table 6208. Master quality control sample table 6208 includes all of the tasks and quality control sampling protocols associated with the production of a biopharmaceutical product. Each task or step in the process time line, the solution preparation schedule or the preparation equipment time line that has an associated quality control protocol 6102 is included in master unit operation list 6206. Each task or step in master unit operation list 6206 also includes a quality control protocol. The quality control protocol parameters of master quality control protocol table 6110 is used to generate master quality

control sample list in step 6202. The master quality control sample list 6202 lists all the codes of the quality control protocols from the master QC protocol table 6110. Step 6204 uses the master quality control sample list to assign sampling assays to each step in master unit operation list 6206 according to which quality control protocol is assigned to each step in master unit operation list 6206. The result of step 6204 is a master QC sample table 6208 which includes all of the steps in the biopharmaceutical production process, solution preparation and equipment preparation as well as their associated quality control protocol and sample list.

FIG. 63 illustrates the process for generating the process equipment quality control time line 6304. Quality control process equipment time line 6304 is a table of all the unit operations associated with process equipment time line 906 as well as the schedule of quality control assays and samples associated with each. Step 6302 generates the process equipment quality control time line 6304. Step 6302 matches the process steps of process equipment 906 with master unit operation list 6206 to determine which assays need to be assigned to the tasks in process equipment time line 906. Step 6302 assigns the quality control samples to be taken in each of the associated tasks from master quality control sample table 6208 to each of the tasks in process equipment time line 906, resulting in process equipment quality control time line 6304.

FIGS 45A-45I illustrate an exemplary process equipment quality control time line 6304. Fig. 45A illustrates unit operations 1A-6A in column 4502. Scheduling for each of the tasks in unit operations 1A-6A is illustrated in columns 4504. Columns 4506 of FIGS. 45A-45B illustrate the quality control assays from master quality control protocol table 6110. Although columns 4506 are empty, if quality control samples were scheduled for unit operations 1A-6A in column 4502, columns 4506 would contain the number of samples to be taken at the scheduled time, as defined in master quality control sample table 6208. FIGS. 45C-45I illustrate the balance of the tasks and unit operations for the process equipment quality control time line 6304.

FIG. 22 illustrates the process for generating the solution preparation equipment quality control time line 2204. Quality control solution preparation equipment time line 2204 is a table of all the tasks associated with solution preparation schedule 3210, as well as the schedule of quality control assays and samples associated with each task. Step 2202 generates the solution preparation equipment quality control time line 2204. Step 2202 matches the solution preparation tasks of solution preparation schedule 3210 with master unit operation list 6206 to determine which assays

need to be assigned to the tasks in solution preparation schedule 3210. Step 2202 assigns the quality control samples to be taken in each of the associated tasks with from master quality control sample table 6208 to each of the tasks in process equipment time line 906, resulting in process equipment quality control time line 2204.

- 5 FIG. 23 illustrates the process for generating preparation equipment quality control time line 2304. Quality control preparation equipment time line 2304 is a table of all the tasks associated with preparation equipment time line 4610, as well as the schedule of quality control assays and samples associated with each task in the preparation equipment protocols. Step 2302 generates the preparation equipment quality control time line 2304. Step 2302 matches the equipment preparation
- 10 tasks of preparation equipment time line 4610 with master unit operation list 6206 to determine which assays need to be assigned to the tasks in preparation equipment time line 4610. Step 2302 assigns the quality control samples to be taken in each of the associated tasks from master quality control sample table 6208 to each of the tasks in process equipment time line 906, resulting in process equipment quality control time line 2304.

15 8.0 *Environment*

The present invention may be implemented using hardware, software or a combination thereof and may be implemented in a computer system or other processing system. In fact, in one embodiment, the invention is directed toward a computer system capable of carrying out the functionality described herein. An example computer system 1901 is shown in FIG. 19. The

20 computer system 1901 includes one or more processors, such as processor 1904. The processor 1904 is connected to a communication bus 1902. Various software embodiments are described in terms of this example computer system. After reading this description, it will become apparent to a person skilled in the relevant art how to implement the invention using other computer systems and/or computer architectures.

- 25 Computer system 1902 also includes a main memory 1906, preferably random access memory (RAM), and can also include a secondary memory 1908. The secondary memory 1908 can include, for example, a hard disk drive 1910 and/or a removable storage drive 1912, representing a floppy disk drive, a magnetic tape drive, an optical disk drive, etc. The removable storage drive

1912 reads from and/or writes to a removable storage unit 1914 in a well known manner. Removable storage unit 1914, represents a floppy disk, magnetic tape, optical disk, etc. which is read by and written to by removable storage drive 1912. As will be appreciated, the removable storage unit 1914 includes a computer usable storage medium having stored therein computer software
5 and/or data.

In alternative embodiments, secondary memory 1908 may include other similar means for allowing computer programs or other instructions to be loaded into computer system 1901. Such means can include, for example, a removable storage unit 1922 and an interface 1920. Examples of such can include a program cartridge and cartridge interface (such as that found in video game
10 devices), a removable memory chip (such as an EPROM, or PROM) and associated socket, and other removable storage units 1922 and interfaces 1920 which allow software and data to be transferred from the removable storage unit 1922 to computer system 1901.

Computer system 1901 can also include a communications interface 1924. Communications interface 1924 allows software and data to be transferred between computer system 1901 and
15 external devices. Examples of communications interface 1924 can include a modem, a network interface (such as an Ethernet card), a communications port, a PCMCIA slot and card, etc. Software and data transferred via communications interface 1924 are in the form of signals which can be electronic, electromagnetic, optical or other signals capable of being received by communications interface 1924. These signals 1926 are provided to communications interface via a channel 1928.
20 This channel 1928 carries signals 1926 and can be implemented using wire or cable, fiber optics, a phone line, a cellular phone link, an RF link and other communications channels.

In this document, the terms "computer program medium" and "computer usable medium" are used to generally refer to media such as removable storage device 1912, a hard disk installed in hard disk drive 1910, and signals 1926. These computer program products are means for providing
25 software to computer system 1901.

Computer programs (also called computer control logic) are stored in main memory and/or secondary memory 1908. Computer programs can also be received via communications interface 1924. Such computer programs, when executed, enable the computer system 1901 to perform the features of the present invention as discussed herein. In particular, the computer programs, when

executed, enable the processor 1904 to perform the features of the present invention. Accordingly, such computer programs represent controllers of the computer system 1901.

In an embodiment where the invention is implemented using software, the software may be stored in a computer program product and loaded into computer system 1901 using removable
5 storage drive 1912, hard drive 1910 or communications interface 1924. The control logic (software), when executed by the processor 1904, causes the processor 1904 to perform the functions of the invention as described herein.

In another embodiment, the invention is implemented primarily in hardware using, for example, hardware components such as application specific integrated circuits (ASICs).
10 Implementation of the hardware state machine so as to perform the functions described herein will be apparent to persons skilled in the relevant art(s).

In yet another embodiment, the invention is implemented using a combination of both hardware and software.

9.0 Conclusion

15 While the invention has been particularly shown and described with reference to preferred embodiments thereof, it will be understood by those skilled in the relevant art(s) that various changes in form and details may be made therein without departing from the spirit and scope of the invention.

What Is Claimed Is:

1. A method for simulating and modeling a batch processing manufacturing facility, comprising the steps of:

- 5 (1) selecting a sequence of unit operations wherein each of said sequence of unit operations has an identifier code;
- (2) selecting a set of scheduling cycles for each of said sequence of unit operations;
- (3) referencing a master table using said identifier code to obtain operational parameters for each of said sequence of unit operations;
- 10 (4) generating a block flow diagram using said sequence of unit operations and said operational parameters; and
- (5) generating a process time line using said operational parameters, said block flow diagram, said set of scheduling cycles for each of said sequence of unit operations, wherein said process time line is used as a tool for batch processing and facility design.

2. The method of claim 1, wherein the batch process manufacturing facility is a
15 biopharmaceutical batch processing facility.

3. A method for scheduling and simulating solution equipment preparation in a batch process manufacturing facility, comprising the steps:

- (1) determining equipment preparation procedures associated with solution preparation equipment;
- 20 (2) generating a master list of soiled process components to be prepared by said equipment preparation procedures;
- (3) generating an equipment preparation load table based on tasks in a biopharmaceutical production process; and
- (4) generating an equipment preparation time line that schedules said solution
25 equipment preparation in said equipment preparation procedures.

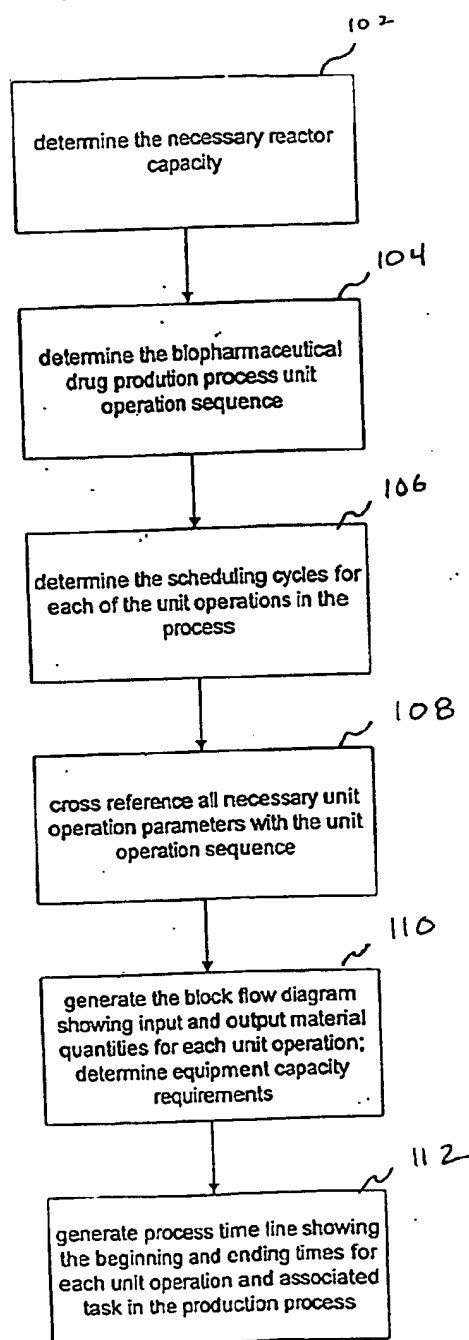


FIG. 1

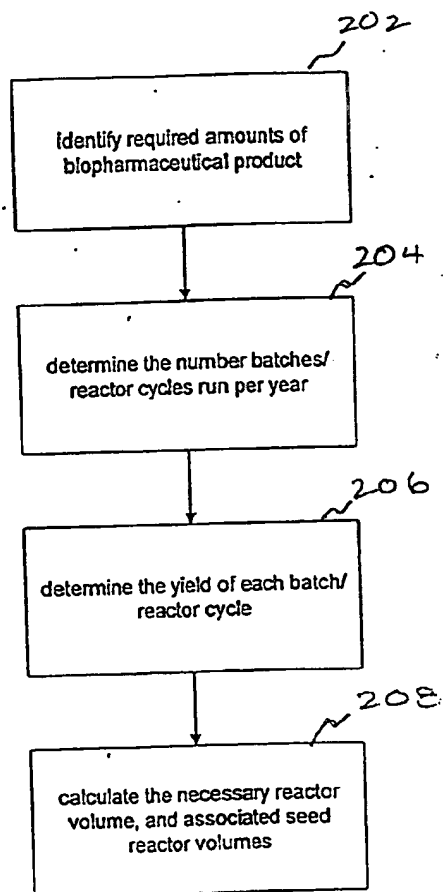
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FIG. 2

Unit Operations List

Microbial Fermentation Process

UOP Seq. No.	Code	Unit Operation Type	Cycles per				Batch				Process				Recovery			
			UnOp		Offset		UnOp		UnOp		UnOp		UnOp		Product		Total Protein	
			Offset (Hrs)	UnOp Start	UnOp End	Offset (Hrs)	UnOp Start	UnOp End	UnOp Start	UnOp End	UnOp Start	UnOp End	UnOp Start	UnOp End	SWR	OAR	SWR	OAR
1	1	Inoculum Prep	1	3	1	6	1	1	1	1	1	1	1	1	100%	100%	100%	100%
2	2	Flask Growth	1	3	1	6	1	1	1	1	1	1	1	1	100%	100%	100%	100%
3	3	Seed Fermentation	1	3	1	6	1	1	1	1	1	1	1	1	100%	100%	100%	100%
4	4	Production Fermentation	1	3	1	6	1	1	1	1	1	1	1	1	85%	85%	85%	85%
5	5	Heat Exchange	1	3	1	6	1	1	1	1	1	1	1	1	100%	100%	100%	100%
6	6	Heat Exchange	1	3	1	6	1	1	1	1	1	1	1	1	100%	100%	100%	100%
7	7	Cont. Centrifugation/Whole Cell Harvest	1	3	1	6	1	1	1	1	1	1	1	1	100%	100%	100%	100%
8	8	Resuspend Cell Paste	1	3	1	6	1	1	1	1	1	1	1	1	80%	80%	80%	80%
9	9	Heat Exchange	1	3	1	6	1	1	1	1	1	1	1	1	100%	100%	100%	100%
10	10	Cell Disruption/High Pressure	1	3	1	6	1	1	1	1	1	1	1	1	100%	100%	100%	100%
11	11	Heat Exchange	1	3	1	6	1	1	1	1	1	1	1	1	76%	76%	76%	76%
12	12	Resuspension/Surfactant	1	3	1	6	1	1	1	1	1	1	1	1	100%	100%	100%	100%
13	13	Cont. Centrifugation/Precipitate Harvest	1	3	1	6	1	1	1	1	1	1	1	1	85%	85%	85%	85%
14	14	Resuspension/Buffer	1	3	1	6	1	1	1	1	1	1	1	1	100%	100%	100%	100%
15	15	Ultrafiltration/Concentration/Dilution	1	3	1	6	1	1	1	1	1	1	1	1	85%	85%	85%	85%
16	16	Microfiltration/Tangential Flow	1	3	1	6	1	1	1	1	1	1	1	1	64%	64%	64%	64%
17	17	Product Adsorption MPLC	1	3	1	6	1	1	1	1	1	1	1	1	85%	85%	85%	85%
18	18	Product Adsorption MPLC	1	3	1	6	1	1	1	1	1	1	1	1	40%	40%	40%	40%
19	19	Ultrafiltration/Flow Dialysis	1	3	1	6	1	1	1	1	1	1	1	1	85%	85%	85%	85%
20	20	Product Adsorption MPLC	1	3	1	6	1	1	1	1	1	1	1	1	39%	39%	39%	39%
21	21	Ultrafiltration/Flow Dialysis	1	3	1	6	1	1	1	1	1	1	1	1	85%	85%	85%	85%
22	22	Product Adsorption MPLC	1	3	1	6	1	1	1	1	1	1	1	1	90%	90%	90%	90%
23	23	Microfiltration/Dead End	1	3	1	6	1	1	1	1	1	1	1	1	85%	85%	85%	85%
302	302	End	1	3	1	6	1	1	1	1	1	1	1	1	328	328	328	328
304	304	End	1	3	1	6	1	1	1	1	1	1	1	1	330	330	330	330
306	306	End	1	3	1	6	1	1	1	1	1	1	1	1	332	332	332	332

FIG. 3

Unit Operations List

Mammalian Cell Culture Process

UOP Seq. No.	Codo	Unit Operation Type	Cycles per				Batch				Process				Recovery			
			UnOp		Offset		UnOp		Offset		UnOp		Offset		UnOp		Offset	
				(Hrs)		(Hrs)	Start	End		(Hrs)	Start	End		(Hrs)	Start	End		(Hrs)
1	4	Initial Seeding	1				1											
2	5	Culture Vessel Split	1				1											
3	5	Culture Vessel Split	1				1											
4	5	Culture Vessel Split	1				1											
5	5	Culture Vessel Split	1				1											
6	6	Spinner Flask Split	1				1											
7	54	Spinner Flask Split	1				1											
8	13	Stirred Tank Reactor	1				1											
9	61	Harvest/Feed	7	24			1											
10	62	Harvest/Feed	1				1											
11	34	MF/Tangential Flow	1				1											
12	36	UF/Concentration	1				1											
13	38	PAC/PLC	1				1											
14	39	PAC/PLC	1				1											
15	36	UF/Concentration	1				1											
16	39	PAC/PLC	1				1											
17	37	UF/Flow Dialysis	1				1											
18	39	PAC/PLC	1				1											
19	33	MF/Dead End	1				1											
20	99	End	1				1											
			402	404	406	408	410	412	414	416	418	420	422	424				

FIG. 4

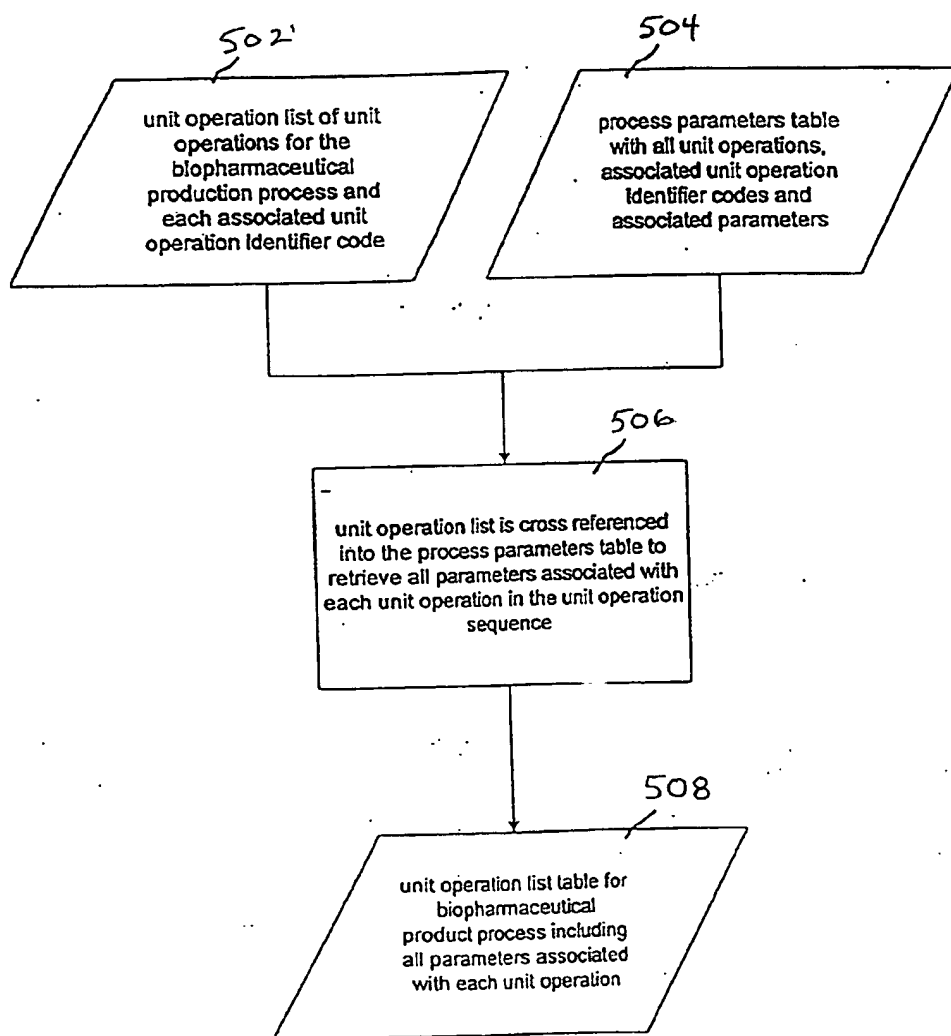
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FIG. 5

504

unit operation id code	Unit operation type	Parameters	solution type	tasks	task duration
1	Inoculum prep	# of flasks, volume of flasks, temperature, agitation, duration, final OD	S-101	setup, preincubation, Incubation, clean up	3, 3, 23, .3 Hrs
2	flask growth	scale up ratio, media volume, temperature, agitation, duration, final OD	S-101	setup, preincubation, Incubation, clean up	1, 1, 23, .3 Hrs
3	fermentation seed	scale up ratio, fermentor working volume, antifoam, base acid, grow temperature, agitation, sparge rate, back pressure, total duration	S-101, 102, 103, 104, 105	setup, preincubation, fermentation, harvest, CIP, SIP, clean up	1, 1, 21, .5, 1, 1, 3 Hrs
4	fermentation production	scale up ratio, fermentor working volume, antifoam A, antifoam B, base, add, grow temperature, agitation, sparge rate, back pressure, total duration, final OK, dry cell mass, product concentration, CIP, SIP	S-101, 102, 103, 104, 105	setup preincubation, fermentation, CIP, SIP, cleanup	.
5	heat exchange	process initial & final temp; utility initial & final temp; process specific heat; design type, step recovery of product, step recovery of T.P., temperature regulation, CIP, SIP		setup, transfer, CIP, SIP, cleanup	.
6	batch centrifugation	system void volume, RCF, time, volume reduction, wash volume, clean, rinse	S-108	setup, centrifugation, wash, CIP, SIP, cleanup	.
7	resolubilization resuspension	reagent/product ratio, filtration solution, resolubilization, agitation, solution name, step recovery of the product, step recovery of T.P., temperature regulation, CIP, SIP	S-107	setup, dilution, agitate, CIP, SIP, clean up	.
8	Cell Disruption High Press. Homogenization	product temperature, utility temperature, void volume, number of passes, pressure, flow rate, temperature increase, wash, rinse, step recovery of product, step recovery of T.P., temperature regulation, CIP	S-107	setup, lysis, CIP, SIP, clean up	.
9	Dilute with Surfactant	reagent product ratio, filtration solution, dilution time, agitation, solution name, step recovery of product, step recovery of T.P., temperature regulation, CIP, SIP	S-108	setup, dilution, agitate, CIP, SIP, clean up	.
10	batch centrifugation precipitate harvest	system void volume, RCF, time, volume reduction, wash volume, clean, rinse, step recovery of product, step recovery of T.P., temperature regulation, CIP, SIP	S-108	setup, centrifugation, wash, CIP, SIP, clean up	.
11	resuspend with chaotrope	reagent/product ratio, filtration solution, resolubilization, agitation, solution name, step recovery of product, step recovery to TP, temperature regulation, CIP, SIP	S-109	setup, flush, prime, concentration, dilution, wash, flush, store, CIP, SIP, cleanup	.
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Fig. 6

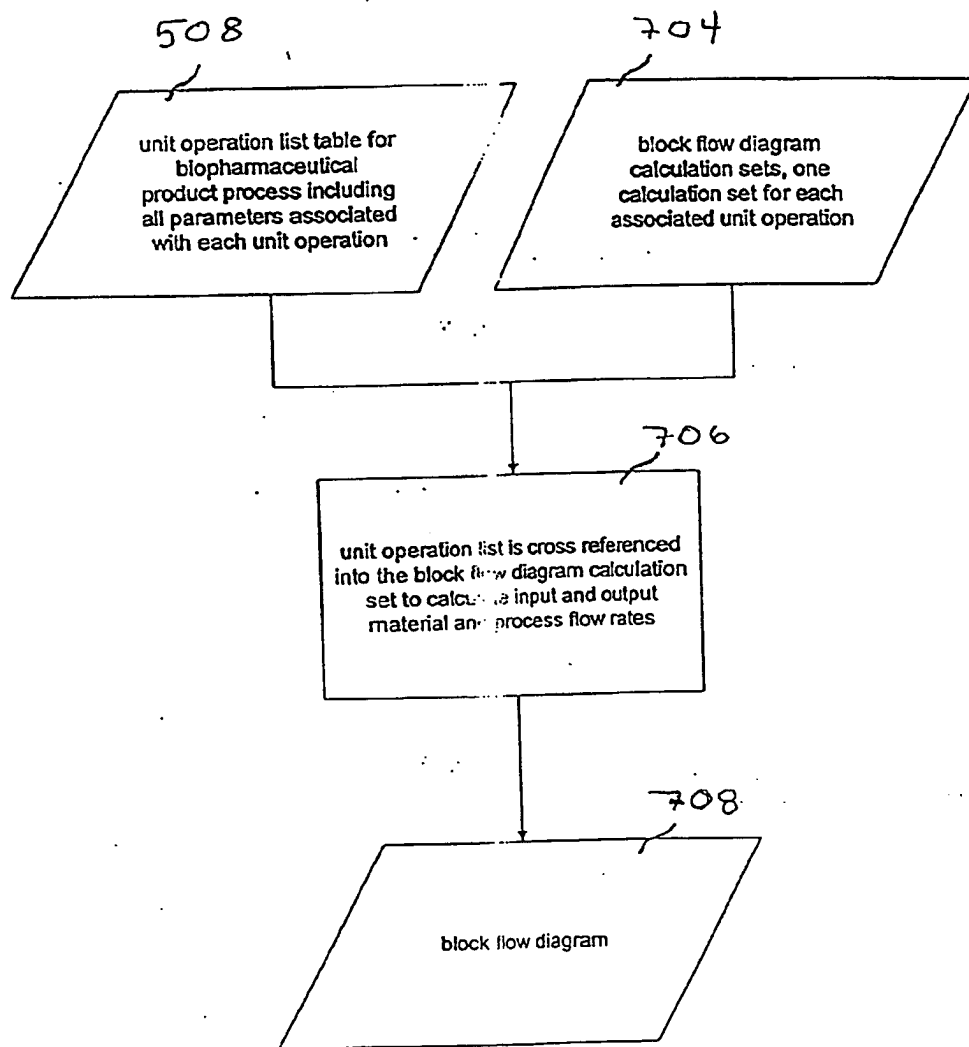
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FIG. 7

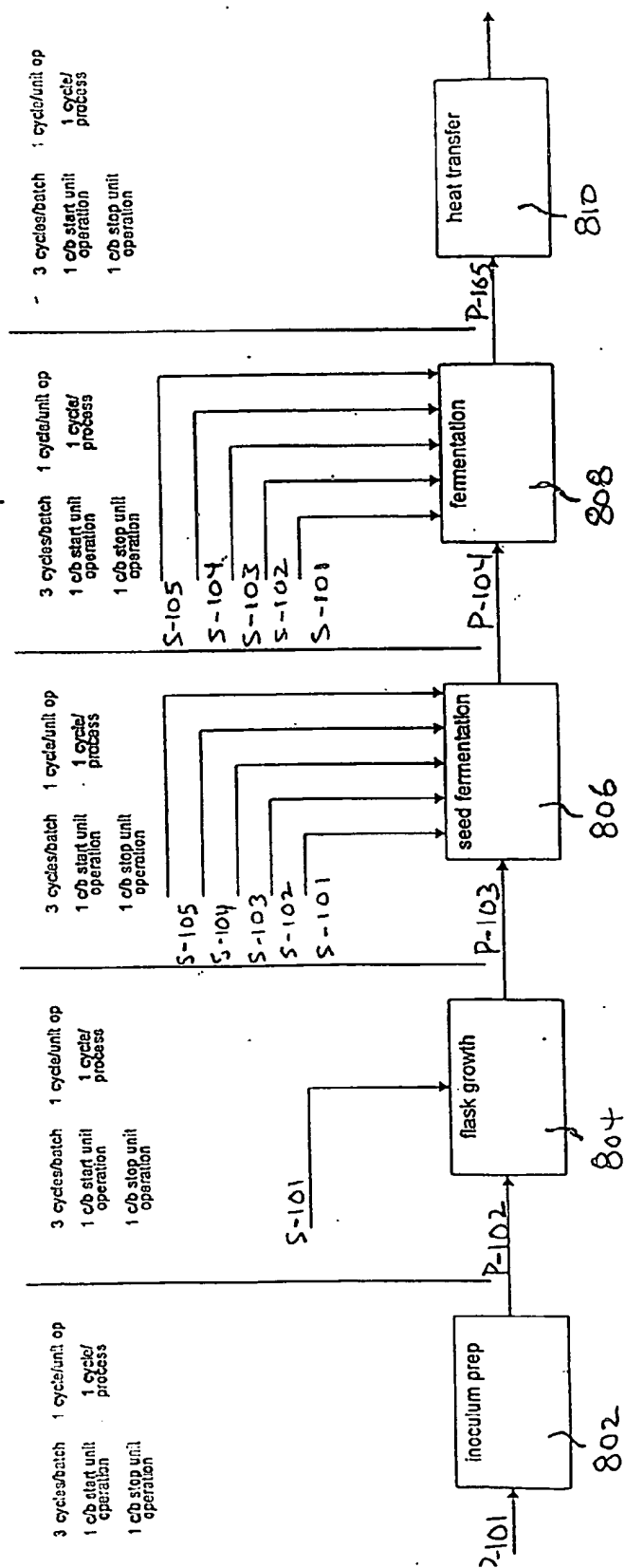


FIG. 8

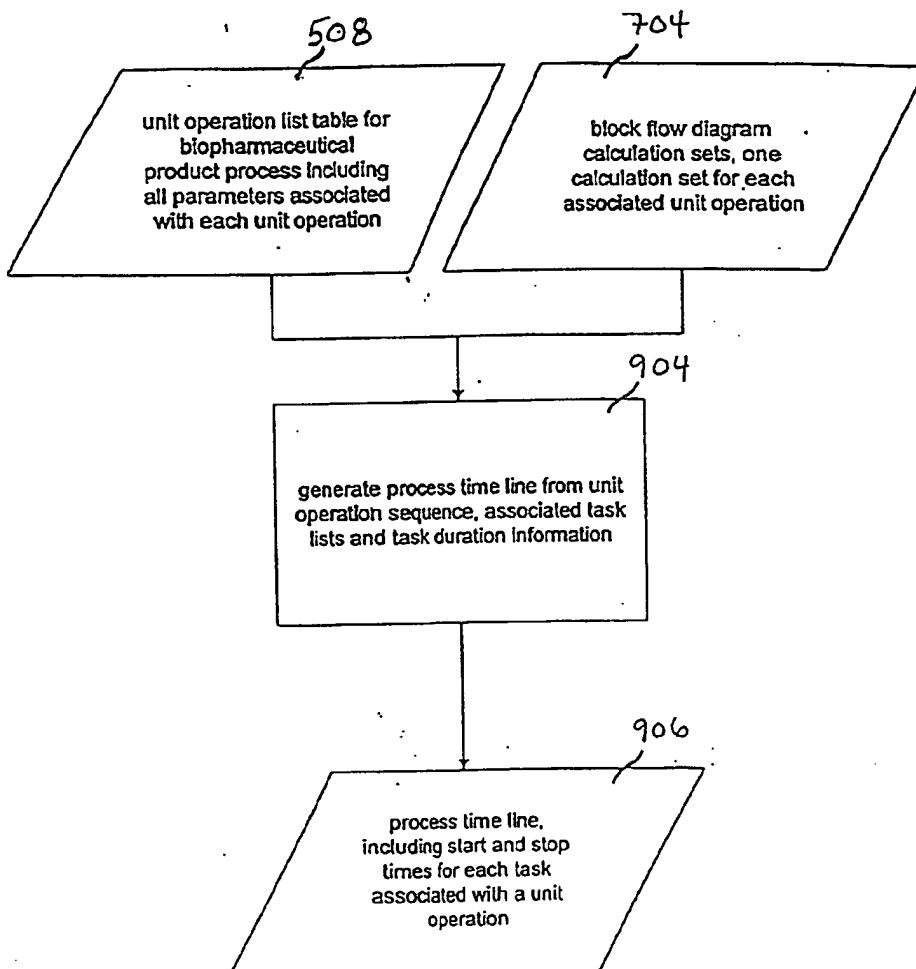
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FIG. 9

Sample Application of Process Design Cycles In Process Scheduling

Microbial Fermentation Process (see unit operation list)

Duration	First Process Cycle		Second Process Cycle	
	Week	Day	Week	Day

Note: None of the unit operations in this process have more than 1 cycle per unit operation
(see unit operation 8 in the mammalian cell culture process for an example of multiple cycles per unit operation)

Unit Operations 1-6 undergo three repetitive cycles per batch as a set before continuing with unit op 7
This translates to three runs on a fermentor with each harvest (unit op 5 & 6) being stored for pooling at unit op 7
Associated with each fermentor run (unit op 4) are the previous steps for inoculation prep (unit ops 1-3)

1/3 fermentation cycles per batch

1	Inoculum Prep	24 hrs	1	Fri - Sat	2	Fri - Sat
2	Flask Growth	24 hrs	2	Sat - Sun	3	Sat - Sun
3	Seed Fermentation	24 hrs	2	Sun - Mon	3	Sun - Mon
4	Production Fermentation	24 hrs	2	Mon - Tue	3	Mon - Tue
5	Heat Exchange	1 hr	2	Tue	3	Tue
6	Centrifugation	1hr	2	Tue	3	Tue

2/3 fermentation cycles per batch

1	Inoculum Prep	24 hrs	2	Sun - Mon	3	Sun - Mon
2	Flask Growth	24 hrs	2	Mon - Tue	3	Mon - Tue
3	Seed Fermentation	24 hrs	2	Tue - Wed	3	Tue - Wed
4	Production Fermentation	24 hrs	2	Wed - Thu	3	Wed - Thu
5	Heat Exchange	1 hr	2	Thu	3	Thu
6	Centrifugation	1hr	2	Thu	3	Thu

3/3 fermentation cycles per batch

1	Inoculum Prep	24 hrs	2	Tue - Wed	3	Tue - Wed
2	Flask Growth	24 hrs	2	Wed - Thu	3	Wed - Thu
3	Seed Fermentation	24 hrs	2	Thu - Fri	3	Thu - Fri
4	Production Fermentation	24 hrs	2	Fri - Sat	3	Fri - Sat
5	Heat Exchange	1 hr	2	Sat	3	Sat
6	Centrifugation	1hr	2	Sat	3	Sat

Unit Operation 7 pools the harvests from the three fermentation cycles above

7	Pool Harvests	3 hr	3	Mon	4	Mon
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Unit Operations 8-10 undergo three repetitive cycles per batch as set before continuing with unit operation 11
This translates to three consecutive passes through cell disruptor (unit op 9) with its associated heat exchangers
(unit op 8 & 10) at the inlet and the outlet of the cell disruptor

1/3 disruption cycles per batch

8	Heat Exchange					
9	Cell Disruption					
10	Heat Exchange	0.5 hr	3	Mon	4	Mon

2/3 disruption cycles per batch

8	Heat Exchange					
9	Cell Disruption					
10	Heat Exchange	0.5 hr	3	Mon	4	Mon

3/3 disruption cycles per batch

8	Heat Exchange					
9	Cell Disruption					
10	Heat Exchange	0.5 hr	3	Mon	4	Mon

FIG. 10

Sample Application of Process Design Cycles in Process Scheduling

Microbial Fermentation Process (see unit operation list)

			First Process Cycle		Second Process Cycle	
Duration			Week	Day	Week	Day
Unit ops 11-12 undergo two repetitive cycles per batch as a set before continuing with unit op 13 This translates to two cycles of resuspending the cell lysate from the cell disruptor in a mild surfactant and reconcentrating the insoluble product to a paste by centrifugation						
1/2 product washing cycles per batch						
11	Resuspension	0.5 hr	3	Mon	4	Mon
12	Centrifugation	1 hr	3	Mon	4	Mon
2/3 product washing cycles per batch						
11	Resuspension	0.5 hr	3	Mon	4	Mon
12	Centrifugation	1 hr	3	Mon	4	Mon
Unit ops 13-22 undergo only one cycle per unit operation each to the end of the process						
13	Resuspension	0.5 hr	3	Mon	4	Mon
14	Buffer Exchange	2 hr	3	Mon	4	Mon
15	Filtration	2 hr	3	Mon	4	Mon
16	Liquid Chromatography	16 hrs	3	Mon - Tue	4	Mon - Tue
17	Liquid Chromatography	4 hrs	3	Tue	4	Tue
18	Buffer Exchange	2 hrs	3	Tue	4	Tue
19	Liquid Chromatography	2 hrs	3	Wed	4	Wed
20	Buffer Exchange	2 hrs	3	Wed	4	Wed
21	Liquid Chromatography	2 hrs	3	Wed	4	Wed
22	Filtration	2 hrs	3	Wed	4	Wed

FIG. 11

Operation		Duration (Hrs.)		Rel. Time Scale (Hrs.)		Abs. Days		Start		Finish		Calculations	
Calc.	Adj.	Prep	Exec.	Comp.	Start	End	Time	Date	Time	Date	Time		
1 A. Inoculum Prep													
1	3.0	0.0	3.0 Hrs	12.5	06/03/98	06/03/98	06:00 AM		06:00 AM		12:30 PM		
2	3.0	0.0	3.0 Hrs	11.5	06/03/98	06/03/98	06:30 AM		06:30 AM		02:30 PM		
3	3.0	0.0	3.0 Hrs	10.5	06/03/98	06/03/98	07:00 AM		07:00 AM		03:00 PM		
4	21.0	0.0	21.0 Hrs	38.5	06/03/98	06/03/98	07:30 PM		07:30 PM		02:30 PM		
5	0.3	0.0	0.3 Hrs	38.8	06/03/98	06/03/98	07:30 PM		07:30 PM		02:30 PM		
6	28.0	0.0	28.0 Hrs	30.3	06/03/98	06/03/98	07:30 PM		07:30 PM		02:30 PM		
7													
2 A. Flask Growth													
8	1.0	0.0	1.0 Hrs	37.5	06/03/98	06/03/98	12:30 PM		06:00 AM		01:30 PM		
9	1.0	0.0	1.0 Hrs	38.5	06/03/98	06/03/98	01:30 PM		06:00 AM		02:30 PM		
10	23.0	0.0	23.0 Hrs	61.5	06/03/98	06/03/98	01:30 PM		06:00 AM		02:30 PM		
11	0.3	0.0	0.3 Hrs	61.8	06/03/98	06/03/98	01:30 PM		06:00 AM		02:30 PM		
12	28.0	0.0	28.0 Hrs	61.5	06/03/98	06/03/98	01:30 PM		06:00 AM		02:30 PM		
13													
3 A. Seed Fermentation													
14	1.0	0.0	1.0 Hrs	60.5	06/03/98	06/03/98	11:30 AM		06:00 AM		12:30 PM		
15	1.0	0.0	1.0 Hrs	61.5	06/03/98	06/03/98	12:30 PM		06:00 AM		01:30 PM		
16	21.0	0.0	21.0 Hrs	83.0	06/03/98	06/03/98	12:30 PM		06:00 AM		01:30 PM		
17	0.5	0.0	0.5 Hrs	83.0	06/03/98	06/03/98	12:30 PM		06:00 AM		01:30 PM		
18	1.0	0.0	1.0 Hrs	83.0	06/03/98	06/03/98	12:30 PM		06:00 AM		01:30 PM		
19	1.0	0.0	1.0 Hrs	83.0	06/03/98	06/03/98	12:30 PM		06:00 AM		01:30 PM		
20	1.0	0.0	1.0 Hrs	83.0	06/03/98	06/03/98	12:30 PM		06:00 AM		01:30 PM		
21	1.0	0.0	1.0 Hrs	83.0	06/03/98	06/03/98	12:30 PM		06:00 AM		01:30 PM		
22	1.0	0.0	1.0 Hrs	83.0	06/03/98	06/03/98	12:30 PM		06:00 AM		01:30 PM		
23	1.0	0.0	1.0 Hrs	83.0	06/03/98	06/03/98	12:30 PM		06:00 AM		01:30 PM		
24	21.0	0.0	21.0 Hrs	83.0	06/03/98	06/03/98	12:30 PM		06:00 AM		01:30 PM		
25													
4 A. Production Fermentation													
26	1.0	0.0	1.0 Hrs	82.0	06/03/98	06/03/98	02:00 AM		06:00 AM		10:00 AM		
27	1.0	0.0	1.0 Hrs	83.0	06/03/98	06/03/98	03:00 AM		06:00 AM		11:00 AM		
28	21.0	0.0	21.0 Hrs	104.0	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
29	1.0	0.0	1.0 Hrs	103.0	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
30	1.0	0.0	1.0 Hrs	103.0	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
31	1.0	0.0	1.0 Hrs	103.0	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
32	1.0	0.0	1.0 Hrs	103.0	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
33	1.0	0.0	1.0 Hrs	103.0	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
34	21.0	0.0	21.0 Hrs	103.0	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
35													
5 A. Heat Exchange													
36	0.50	0.0	0.5 Hrs	104.5	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
37	1.00	0.0	1.0 Hrs	104.5	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
38	1.00	0.0	1.0 Hrs	104.5	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
39	1.00	0.0	1.0 Hrs	104.5	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
40	1.00	0.0	1.0 Hrs	104.5	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
41	1.00	0.0	1.0 Hrs	104.5	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
42	1.00	0.0	1.0 Hrs	104.5	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
43	5.0	0.0	5.0 Hrs	104.5	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
44													
6 A. Cont. Cult/Solids													
45	1.00	0.0	1.0 Hrs	103.0	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
46	1.00	0.0	1.0 Hrs	103.0	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
47	0.10	0.0	0.1 Hrs	104.1	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
48	0.10	0.0	0.1 Hrs	104.1	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
49	0.10	0.0	0.1 Hrs	104.1	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
50	0.10	0.0	0.1 Hrs	104.1	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
51	1.00	0.0	1.0 Hrs	107.4	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
52	0.50	0.0	0.5 Hrs	107.4	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
53	3.85	0.0	3.85 Hrs	104.1	06/03/98	06/03/98	03:00 AM		06:00 AM		03:00 AM		
54													
7 B. Inoculum Prep													
55	1.0	0.0	1.0 Hrs	14.5	06/03/98	06/03/98	01:30 PM		06:00 AM		02:30 PM		
56	1.0	0.0	1.0 Hrs	15.5	06/03/98	06/03/98	02:30 PM		06:00 AM		03:30 PM		
57													
58													

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FIG. 12A

Process Time Line										Start				Finish				Calculations
Duration (Hrs)										Rel. Time Scale (Hrs)		Abs. Days		Time		Date		
Operation		Calc.	Adj.	Prep	Exec.	Comp.	Start	End		Prep	Exec.	Start	End	Time	Date	Time	Date	
Inoculation		23.0	0.0	23.0 Hrs	13.5		06/04/98	06/04/98		13.5		06/04/98	06/04/98	06/04/98	06/04/98	06/04/98	06/04/98	
Clean Up		0.3	0.0	0.3 Hrs														
Subtotal		23.0		23.0 Hrs	13.5													
2 D Flask Growth																		
Set Up		1.0	0.0	1.0 Hrs	37.6		06/04/98	06/04/98						06/04/98	06/04/98	06/04/98	06/04/98	
Preinoculation		1.0	0.0	1.0 Hrs	38.5		06/04/98	06/04/98						06/04/98	06/04/98	06/04/98	06/04/98	
Inoculation		23.0	0.0	23.0 Hrs	61.6		06/04/98	06/04/98						06/04/98	06/04/98	06/04/98	06/04/98	
Clean Up		0.3	0.0	0.3 Hrs										06/04/98	06/04/98	06/04/98	06/04/98	
Subtotal		25.0		25.0 Hrs	61.6													
3 D Seed Fermentation																		
Set Up		1.0	0.0	1.0 Hrs	60.5		06/05/98	06/05/98						06/05/98	06/05/98	06/05/98	06/05/98	
Preinoculation		1.0	0.0	1.0 Hrs	61.5		06/05/98	06/05/98						06/05/98	06/05/98	06/05/98	06/05/98	
Fermentation		21.0	0.0	21.0 Hrs	82.5		06/05/98	06/05/98						06/05/98	06/05/98	06/05/98	06/05/98	
Harvest		0.5	0.0	0.5 Hrs	83.0		06/05/98	06/05/98						06/05/98	06/05/98	06/05/98	06/05/98	
CIP		1.0	0.0	1.0 Hrs										06/05/98	06/05/98	06/05/98	06/05/98	
SIP		1.0	0.0	1.0 Hrs										06/05/98	06/05/98	06/05/98	06/05/98	
Clean Up		1.0	0.0	1.0 Hrs										06/05/98	06/05/98	06/05/98	06/05/98	
Subtotal		24.0		24.0 Hrs	83.0												60.0 L 1.7 LPM = 0.50 Hrs	
4 D Production Fermentation																		
Set Up		1.0	0.0	1.0 Hrs	82.0		06/06/98	06/06/98						06/06/98	06/06/98	06/06/98	06/06/98	
Preinoculation		1.0	0.0	1.0 Hrs	83.0		06/06/98	06/06/98						06/06/98	06/06/98	06/06/98	06/06/98	
Fermentation		21.0	0.0	21.0 Hrs	104.0		06/06/98	06/06/98						06/06/98	06/06/98	06/06/98	06/06/98	
CIP		1.0	0.0	1.0 Hrs										06/06/98	06/06/98	06/06/98	06/06/98	
SIP		1.0	0.0	1.0 Hrs										06/06/98	06/06/98	06/06/98	06/06/98	
Clean Up		2.0	0.0	2.0 Hrs										06/06/98	06/06/98	06/06/98	06/06/98	
Subtotal		27.0		27.0 Hrs	104.0												692.1 L 0.4 LPM = 1.00 Hrs	
5 D Post Exchange																		
Set Up		0.50	0.0	0.5 Hrs	104.5		06/07/98	06/07/98						06/07/98	06/07/98	06/07/98	06/07/98	
Transfer		1.00	0.0	1.0 Hrs										06/07/98	06/07/98	06/07/98	06/07/98	
CIP		1.0	0.0	1.0 Hrs										06/07/98	06/07/98	06/07/98	06/07/98	
SIP		1.0	0.0	1.0 Hrs										06/07/98	06/07/98	06/07/98	06/07/98	
Clean Up		2.0	0.0	2.0 Hrs										06/07/98	06/07/98	06/07/98	06/07/98	
Subtotal		5.0		5.0 Hrs	105.0													
6 D Cont. Centrifugation																		
Set Up		1.00	0.0	1.0 Hrs	105.0		06/07/98	06/07/98						06/07/98	06/07/98	06/07/98	06/07/98	
Centrifugation		1.00	0.0	1.0 Hrs										06/07/98	06/07/98	06/07/98	06/07/98	
Wash		0.10	0.0	0.1 Hrs										06/07/98	06/07/98	06/07/98	06/07/98	
CIP		0.25	0.0	0.2 Hrs										06/07/98	06/07/98	06/07/98	06/07/98	
SIP		1.00	0.0	1.0 Hrs										06/07/98	06/07/98	06/07/98	06/07/98	
Clean Up		0.50	0.0	0.5 Hrs										06/07/98	06/07/98	06/07/98	06/07/98	
Sub Total		3.85		3.85 Hrs	105.1												692.1 L 0.4 LPM = 1.00 Hrs 1.0 L 0.2 LPM = 0.10 Hrs 20.0 L 1.3 LPM = 0.25 Hrs	
7 D Inoculum Prep																		
Set Up		1.0	0.0	1.0 Hrs	14.5		06/07/98	06/07/98						06/07/98	06/07/98	06/07/98	06/07/98	
Preinoculation		1.0	0.0	1.0 Hrs	15.5		06/07/98	06/07/98						06/07/98	06/07/98	06/07/98	06/07/98	
Inoculation		23.0	0.0	23.0 Hrs	39.5		06/07/98	06/07/98						06/07/98	06/07/98	06/07/98	06/07/98	
Clean Up		0.3	0.0	0.3 Hrs										06/07/98	06/07/98	06/07/98	06/07/98	
Subtotal		25.0		25.0 Hrs	39.5													

Fig. 12B

Line	Operation	Duration (Hrs.)			Rel. Time Scale (Hrs.)			Start			Finish			Calculations
		Cat.	AD	Adj.	Prep	Exec.	Comp.	Start	End	Date	Time	Date	Time	
114	2 C Plant Growth					13.5				08/07/98	08:30 AM			
115	Set Up	1.0	0.0	1.0 Hrs	37.3			1.57	1.58	08/04/98	12:30 PM	08/04/98	01:50 PM	
116	Preinoculation	1.0	0.0	1.0 Hrs	34.5			1.58	1.60	08/04/98	01:30 PM	08/04/98	02:30 PM	
117	Inoculation	23.0	0.0	23.0 Hrs		61.5		2.56	2.58	08/04/98	02:30 PM	08/04/98	01:30 PM	
118	Clean Up	0.3	0.0	0.3 Hrs			61.8	2.56	2.57	08/05/98	01:30 PM	08/05/98	01:45 PM	
119	Subtotal	25.0		25.0 Hrs		61.3								
120	3 C Seed Fermentation													
121	Set Up	1.0	0.0	1.0 Hrs	50.5			2.48	2.51	08/05/98	11:30 AM	08/05/98	12:30 PM	
122	Preinoculation	1.0	0.0	1.0 Hrs	81.5			2.51	2.54	08/05/98	12:30 PM	08/05/98	01:30 PM	
123	Fermentation	21.0	0.0	21.0 Hrs		82.5		2.54	2.58	08/05/98	01:30 PM	08/05/98	10:40 AM	
124	Harvest	0.5	0.0	0.5 Hrs		83.0		2.58	2.59	08/05/98	10:40 AM	08/05/98	11:30 AM	
125	CIP	1.0	0.0	1.0 Hrs			83.5	2.59	2.61	08/05/98	11:30 AM	08/05/98	12:30 PM	
126	SIP	1.0	0.0	1.0 Hrs			84.0	2.61	2.62	08/05/98	12:30 PM	08/05/98	01:30 PM	
127	Clean Up	3.0	0.0	3.0 Hrs			87.5	2.62	2.65	08/05/98	01:30 PM	08/05/98	02:30 PM	
128	Subtotal	28.5		28.5 Hrs		83.0								
129	4 C Production Fermentation													
130	Set Up	1.0	0.0	1.0 Hrs	92.0			3.38	3.42	08/06/98	09:30 AM	08/06/98	10:30 AM	
131	Preinoculation	1.0	0.0	1.0 Hrs	93.0			3.42	3.48	08/06/98	10:30 AM	08/06/98	11:30 AM	
132	Fermentation	21.0	0.0	21.0 Hrs		104.0		3.48	4.33	08/06/98	11:30 AM	08/07/98	08:30 AM	
133	CIP	1.0	0.0	1.0 Hrs			105.0	4.33	4.34	08/07/98	08:30 AM	08/07/98	09:30 AM	
134	SIP	1.0	0.0	1.0 Hrs			106.0	4.34	4.42	08/07/98	09:30 AM	08/07/98	10:30 AM	
135	Clean Up	2.0	0.0	2.0 Hrs			108.0	4.42	4.50	08/07/98	10:30 AM	08/07/98	12:30 PM	
136	Subtotal	27.0		27.0 Hrs		104.0								
137	5 C Heat Exchange													
138	Set Up	0.50	0.0	0.5 Hrs	104.5			4.33	4.35	08/07/98	08:30 AM	08/07/98	09:30 AM	
139	Transfer	1.00	0.0	1.0 Hrs				4.35	4.38	08/07/98	09:30 AM	08/07/98	10:30 AM	
140	CIP	1.0	0.0	1.0 Hrs			106.0	4.38	4.42	08/07/98	10:30 AM	08/07/98	11:30 AM	
141	SIP	1.0	0.0	1.0 Hrs			107.0	4.42	4.48	08/07/98	11:30 AM	08/07/98	12:30 PM	
142	Clean Up	2.0	0.0	2.0 Hrs			109.0	4.48	4.54	08/07/98	12:30 PM	08/07/98	01:30 PM	
143	Subtotal	5.0		5.0 Hrs		105.0								
144	6 C Cont. Centrifuge													
145	Set Up	1.00	0.0	1.0 Hrs	105.0			4.33	4.35	08/07/98	08:30 AM	08/07/98	09:30 AM	
146	Centrifugation	1.00	0.0	1.0 Hrs				4.35	4.42	08/07/98	09:30 AM	08/07/98	10:30 AM	
147	Wash	0.10	0.0	0.1 Hrs	106.1			4.42	4.43	08/07/98	10:30 AM	08/07/98	11:30 AM	
148	CIP	0.23	0.0	0.3 Hrs			106.4	4.43	4.47	08/07/98	11:30 AM	08/07/98	12:30 PM	
149	SIP	1.00	0.0	1.0 Hrs			107.4	4.47	4.49	08/07/98	12:30 PM	08/07/98	01:30 PM	
150	Clean Up	0.50	0.0	0.5 Hrs			107.9	4.49	4.51	08/07/98	01:30 PM	08/07/98	02:30 PM	
151	Sub Total	3.83		3.83 Hrs		106.1								
152	7 A Recirculation													
153	Set Up	1.00	0.0	1.0 Hrs	106.1			4.35	4.42	08/07/98	09:30 AM	08/07/98	10:30 AM	
154	Disinfection	0.50	0.0	0.5 Hrs				4.42	4.44	08/07/98	10:30 AM	08/07/98	11:30 AM	
155	Aquas	1.00	0.0	1.0 Hrs			107.5	4.44	4.48	08/07/98	11:30 AM	08/07/98	12:30 PM	
156	CIP	1.00	0.0	1.0 Hrs			108.0	4.48	4.53	08/07/98	12:30 PM	08/07/98	01:30 PM	
157	SIP	1.00	0.0	1.0 Hrs			109.0	4.53	4.57	08/07/98	01:30 PM	08/07/98	02:30 PM	
158	Clean Up	3.50	0.0	3.50 Hrs			110.0	4.57	4.61	08/07/98	02:30 PM	08/07/98	03:30 PM	
159	Subtotal	9.50		9.50 Hrs		107.0								
160	8 A Heat Exchange													
161	Set Up	1.00	0.0	1.0 Hrs	106.1			4.35	4.42	08/07/98	09:30 AM	08/07/98	10:30 AM	
162	Disinfection	0.50	0.0	0.5 Hrs				4.42	4.44	08/07/98	10:30 AM	08/07/98	11:30 AM	
163	Aquas	1.00	0.0	1.0 Hrs			107.5	4.44	4.48	08/07/98	11:30 AM	08/07/98	12:30 PM	
164	CIP	1.00	0.0	1.0 Hrs			108.0	4.48	4.53	08/07/98	12:30 PM	08/07/98	01:30 PM	
165	SIP	1.00	0.0	1.0 Hrs			109.0	4.53	4.57	08/07/98	01:30 PM	08/07/98	02:30 PM	
166	Clean Up	3.50	0.0	3.50 Hrs			110.0	4.57	4.61	08/07/98	02:30 PM	08/07/98	03:30 PM	
167	Subtotal	9.50		9.50 Hrs		107.0								

FIG. 12C

Process Time Line

Operation	Duration (hrs)		Rel. Time Scale (hrs)		Abs. Drg		Start		Finish		Calculations
	Calc	Adj.	Prep	Exec	Compd	Start	End	Time	Date	Time	
Set Up	0.50	0.0	0.5 Hrs	107.9	15.3	4.48	4.48	06:07:00	06:07:00	11:54 AM	60.5 L @ 3.7 LPH • 0.30 Hrs
Transfer	0.30	0.0	0.3 Hrs	107.9		4.48	4.48	06:07:00	06:07:00	11:54 AM	
CIP	0.0	0.0	0.0 Hrs			4.48	4.48	06:07:00	06:07:00	11:54 AM	
SP	0.0	0.0	0.0 Hrs			4.48	4.48	06:07:00	06:07:00	11:54 AM	
Clean Up	0.0	0.0	0.0 Hrs			4.48	4.48	06:07:00	06:07:00	11:54 AM	60.5 L @ 3.7 LPH • 0.30 Hrs
Subtotal	0.80	0.0	0.8 Hrs	107.9		4.48	4.48	06:07:00	06:07:00	11:54 AM	
9 A Homogenization											
Set Up	0.25	0.0	0.3 Hrs	107.9		4.49	4.50	06:07:00	06:07:00	11:54 AM	60.5 L @ 3.7 LPH • 0.30 Hrs
Transfer	0.08	0.0	0.7 Hrs	108.6		4.50	4.52	06:07:00	06:07:00	11:54 AM	
CIP	0.0	0.0	0.0 Hrs			4.52	4.52	06:07:00	06:07:00	11:54 AM	
SP	0.0	0.0	0.0 Hrs			4.52	4.52	06:07:00	06:07:00	11:54 AM	
Clean Up	0.0	0.0	0.0 Hrs			4.52	4.52	06:07:00	06:07:00	11:54 AM	60.5 L @ 3.7 LPH • 0.30 Hrs
Subtotal	0.33	0.0	0.3 Hrs	108.6		4.52	4.52	06:07:00	06:07:00	11:54 AM	
10 A Heat Exchange											
Set Up	0.50	0.0	0.5 Hrs	108.6		4.50	4.52	06:07:00	06:07:00	12:34 PM	60.5 L @ 3.7 LPH • 0.30 Hrs
Transfer	0.30	0.0	0.3 Hrs	108.9		4.52	4.54	06:07:00	06:07:00	12:34 PM	
CIP	0.0	0.0	0.0 Hrs			4.54	4.54	06:07:00	06:07:00	12:34 PM	
SP	0.0	0.0	0.0 Hrs			4.54	4.54	06:07:00	06:07:00	12:34 PM	
Clean Up	0.0	0.0	0.0 Hrs			4.54	4.54	06:07:00	06:07:00	12:34 PM	60.5 L @ 3.7 LPH • 0.30 Hrs
Subtotal	0.80	0.0	0.8 Hrs	108.9		4.54	4.54	06:07:00	06:07:00	12:34 PM	
8 B Heat Exchange											
Set Up	0.00	0.0	0.0 Hrs	108.0		4.54	4.54	06:07:00	06:07:00	12:34 PM	60.5 L @ 3.7 LPH • 0.30 Hrs
Transfer	0.30	0.0	0.3 Hrs	109.2		4.54	4.55	06:07:00	06:07:00	12:34 PM	
CIP	0.0	0.0	0.0 Hrs			4.55	4.55	06:07:00	06:07:00	12:34 PM	
SP	0.0	0.0	0.0 Hrs			4.55	4.55	06:07:00	06:07:00	12:34 PM	
Clean Up	0.0	0.0	0.0 Hrs			4.55	4.55	06:07:00	06:07:00	12:34 PM	60.5 L @ 3.7 LPH • 0.30 Hrs
Subtotal	0.30	0.0	0.3 Hrs	109.2		4.55	4.55	06:07:00	06:07:00	12:34 PM	
9 B Homogenization											
Set Up	0.00	0.0	0.0 Hrs	109.2		4.55	4.55	06:07:00	06:07:00	12:34 PM	60.5 L @ 3.7 LPH • 0.30 Hrs
Transfer	0.08	0.0	0.7 Hrs	109.9		4.55	4.55	06:07:00	06:07:00	12:34 PM	
CIP	0.0	0.0	0.0 Hrs			4.55	4.55	06:07:00	06:07:00	12:34 PM	
SP	0.0	0.0	0.0 Hrs			4.55	4.55	06:07:00	06:07:00	12:34 PM	
Clean Up	0.0	0.0	0.0 Hrs			4.55	4.55	06:07:00	06:07:00	12:34 PM	60.5 L @ 3.7 LPH • 0.30 Hrs
Subtotal	0.16	0.0	0.1 Hrs	109.9		4.55	4.55	06:07:00	06:07:00	12:34 PM	
10 B Heat Exchange											
Set Up	0.50	0.0	0.5 Hrs	109.9		4.59	4.59	06:07:00	06:07:00	01:21 PM	60.5 L @ 3.7 LPH • 0.30 Hrs
Transfer	0.30	0.0	0.3 Hrs	110.2		4.59	4.59	06:07:00	06:07:00	01:21 PM	
CIP	0.0	0.0	0.0 Hrs			4.59	4.59	06:07:00	06:07:00	01:21 PM	
SP	0.0	0.0	0.0 Hrs			4.59	4.59	06:07:00	06:07:00	01:21 PM	
Clean Up	0.0	0.0	0.0 Hrs			4.59	4.59	06:07:00	06:07:00	01:21 PM	60.5 L @ 3.7 LPH • 0.30 Hrs
Subtotal	0.80	0.0	0.8 Hrs	110.2		4.59	4.59	06:07:00	06:07:00	01:21 PM	
8 C Heat Exchange											
Set Up	0.00	0.0	0.0 Hrs	110.2		4.59	4.59	06:07:00	06:07:00	01:21 PM	60.5 L @ 3.7 LPH • 0.30 Hrs
Transfer	0.30	0.0	0.3 Hrs	110.5		4.59	4.60	06:07:00	06:07:00	01:21 PM	
CIP	0.0	0.0	0.0 Hrs			4.60	4.60	06:07:00	06:07:00	01:21 PM	
SP	0.0	0.0	0.0 Hrs			4.60	4.60	06:07:00	06:07:00	01:21 PM	
Clean Up	0.0	0.0	0.0 Hrs			4.60	4.60	06:07:00	06:07:00	01:21 PM	60.5 L @ 3.7 LPH • 0.30 Hrs
Subtotal	0.30	0.0	0.3 Hrs	110.5		4.60	4.60	06:07:00	06:07:00	01:21 PM	
21											
22											
23											
24											

FIG. 12D

Operation	Duration (Hrs.)		Rel. Time Scale (Hrs)	Abs. Days		Start		Finish		Calculations	
	Calc.	Adj.		Prep.	Exec.	Comp.	Start	End	Time		Date
1 C Homogenization											
225											
226											
227	0.00	0.0	0.0 Hrs	110.5		4.00	4.00	06:07:00	06:07:00	02:27 PM	69.5 L @ 1.0 LPH = 0.60 Hrs
228	0.68	0.0	0.7 Hrs			4.00	4.07	06:07:00	06:07:00	03:07 PM	
229	1.0	0.0	1.0 Hrs			4.00	4.07	06:07:00	06:07:00	04:07 PM	
230	1.0	0.0	1.0 Hrs			4.00	4.07	06:07:00	06:07:00	05:07 PM	
231	1.0	0.0	1.0 Hrs			4.00	4.07	06:07:00	06:07:00	06:07 PM	
232	3.7		3.7 Hrs	111.1							
233											
10 C Heat Exchange											
234											
235	0.00	0.0	0.0 Hrs	111.1		4.00	4.00	06:07:00	06:07:00	03:07 PM	69.0 L @ 3.0 LPH = 0.30 Hrs
236	0.10	0.0	0.3 Hrs			4.00	4.04	06:07:00	06:07:00	03:23 PM	
237	1.0	0.0	1.0 Hrs			4.00	4.08	06:07:00	06:07:00	04:23 PM	
238	1.0	0.0	1.0 Hrs			4.00	4.08	06:07:00	06:07:00	05:23 PM	
239	1.0	0.0	1.0 Hrs			4.00	4.08	06:07:00	06:07:00	06:23 PM	
240	3.3		3.3 Hrs	111.4							
241											
11 A Recirculation											
242											
243	1.0	0.0	1.0 Hrs	109.9		4.00	4.04	06:07:00	06:07:00	12:53 PM	204.0 L @ 0.9 LPH = 0.50 Hrs
244	0.5	0.0	0.5 Hrs			4.00	4.05	06:07:00	06:07:00	01:23 PM	
245	0.5	0.0	0.5 Hrs	109.4		4.00	4.05	06:07:00	06:07:00	01:53 PM	
246	0.5	0.0	0.5 Hrs			4.00	4.05	06:07:00	06:07:00	01:53 PM	
247	0.5	0.0	0.5 Hrs	109.9		4.00	4.05	06:07:00	06:07:00	01:53 PM	
248	0.5	0.0	0.5 Hrs			4.00	4.05	06:07:00	06:07:00	01:53 PM	
249	0.5	0.0	0.5 Hrs	109.9		4.00	4.05	06:07:00	06:07:00	01:53 PM	
250	0.5	0.0	0.5 Hrs			4.00	4.05	06:07:00	06:07:00	01:53 PM	
251	2.0		2.0 Hrs	109.9							
252											
12 A Cent. Centrifuges											
253											
254	1.0	0.0	1.0 Hrs	109.9		4.00	4.04	06:07:00	06:07:00	01:53 PM	274.0 L @ 0.2 LPH = 0.60 Hrs
255	0.5	0.0	0.5 Hrs			4.00	4.05	06:07:00	06:07:00	02:23 PM	
256	0.5	0.0	0.5 Hrs	110.4		4.00	4.05	06:07:00	06:07:00	02:23 PM	
257	0.5	0.0	0.5 Hrs	110.5		4.00	4.05	06:07:00	06:07:00	02:23 PM	
258	0.5	0.0	0.5 Hrs			4.00	4.05	06:07:00	06:07:00	02:23 PM	
259	0.5	0.0	0.5 Hrs	110.5		4.00	4.05	06:07:00	06:07:00	02:23 PM	
260	0.5	0.0	0.5 Hrs			4.00	4.05	06:07:00	06:07:00	02:23 PM	
261	0.5	0.0	0.5 Hrs	110.5		4.00	4.05	06:07:00	06:07:00	02:23 PM	
262	1.0	0.0	1.0 Hrs	110.5							
263											
11 B Recirculation											
264											
265	0.0	0.0	0.0 Hrs	110.6		4.00	4.00	06:07:00	06:07:00	02:23 PM	204.0 L @ 0.9 LPH = 0.50 Hrs
266	0.5	0.0	0.5 Hrs			4.00	4.02	06:07:00	06:07:00	02:53 PM	
267	0.5	0.0	0.5 Hrs	111.0		4.00	4.02	06:07:00	06:07:00	03:13 PM	
268	0.5	0.0	0.5 Hrs	111.2		4.00	4.02	06:07:00	06:07:00	04:13 PM	
269	0.5	0.0	0.5 Hrs			4.00	4.02	06:07:00	06:07:00	05:13 PM	
270	1.0	0.0	1.0 Hrs			4.00	4.02	06:07:00	06:07:00	06:13 PM	
271	1.0	0.0	1.0 Hrs			4.00	4.02	06:07:00	06:07:00	06:13 PM	
272	1.0	0.0	1.0 Hrs			4.00	4.02	06:07:00	06:07:00	06:13 PM	
273	3.0		3.0 Hrs	111.2							
274											
12 B Cent. Centrifuges											
275											
276	1.0	0.0	1.0 Hrs	111.2		4.00	4.00	06:07:00	06:07:00	02:13 PM	274.0 L @ 0.2 LPH = 0.60 Hrs
277	0.5	0.0	0.5 Hrs			4.00	4.00	06:07:00	06:07:00	02:13 PM	
278	0.5	0.0	0.5 Hrs	111.7		4.00	4.00	06:07:00	06:07:00	03:13 PM	
279	0.5	0.0	0.5 Hrs	111.5		4.00	4.00	06:07:00	06:07:00	04:13 PM	
280	0.5	0.0	0.5 Hrs			4.00	4.00	06:07:00	06:07:00	05:13 PM	
281	0.5	0.0	0.5 Hrs	112.1		4.00	4.00	06:07:00	06:07:00	06:13 PM	
282	0.5	0.0	0.5 Hrs			4.00	4.00	06:07:00	06:07:00	06:13 PM	
283	0.5	0.0	0.5 Hrs	112.1		4.00	4.00	06:07:00	06:07:00	06:13 PM	
284	1.0	0.0	1.0 Hrs								
285	1.0	0.0	1.0 Hrs								
286	3.0		3.0 Hrs								
287											
13 A Cent. Centrifuges											
288											
289	1.0	0.0	1.0 Hrs								
290	0.5	0.0	0.5 Hrs								
291	0.5	0.0	0.5 Hrs								
292	0.5	0.0	0.5 Hrs								
293	0.5	0.0	0.5 Hrs								
294	0.5	0.0	0.5 Hrs								
295	1.0	0.0	1.0 Hrs								
296	1.0	0.0	1.0 Hrs								
297	3.0		3.0 Hrs								
298											
13 B Cent. Centrifuges											
299											
300	1.0	0.0	1.0 Hrs								
301	0.5	0.0	0.5 Hrs								
302	0.5	0.0	0.5 Hrs								
303	0.5	0.0	0.5 Hrs								
304	0.5	0.0	0.5 Hrs								
305	1.0	0.0	1.0 Hrs								
306	1.0	0.0	1.0 Hrs								
307	3.0		3.0 Hrs								
308											

FIG. 12E

Operation	Duration (Hrs.)		Rel. Time State (Hrs.)		Abs. Days		Start		Finish		Calculations
	Calc.	Adj.	Prep.	Exec.	Comp.	Start	End	Date	Time	Date	
216 Set Up	1.0	0.0	110.5	15.5		4.69	4.69	06/07/96	01:23 PM	06/07/96	0.07 L @ 2.0 LPM
217 Deaeration	0.5	0.0	111.0			4.70	4.72	06/07/96	02:28 PM	06/07/96	0.50 Hrs. 23.60 Hrs.
218 Aeration	10.0	0.0	119.0	179.0		4.82	5.37	06/07/96	05:59 AM	06/07/96	
219 CIP	1.0	0.0			130.0	5.37	5.42	06/07/96	06:29 AM	06/07/96	
220 SIP	1.0	0.0			131.0	5.42	5.48	06/07/96	06:39 AM	06/07/96	
221 Clean Up	1.0	0.0			132.0	5.48	5.50	06/07/96	06:59 AM	06/07/96	
222 Subtotal	22.5			179.2				06/07/96	06:59 AM	06/07/96	
223 14 A Concentration											20.99 SF
224 Set Up	1.0	0.0	127.0			5.51	5.52	06/07/96	07:23 AM	06/07/96	3.0 LPSFH or 1.35 LPM
225 Flush	0.7	0.0	128.3			5.53	5.57	06/07/96	07:33 AM	06/07/96	3.0 LPSFH or 1.35 LPM
226 Prime	0.7	0.0	129.0			5.57	5.62	06/07/96	07:43 AM	06/07/96	3.0 LPSFH or 1.35 LPM
227 Concentration	1.0	0.0	130.0	130.0		5.62	5.67	06/07/96	07:53 AM	06/07/96	3.0 LPSFH or 1.35 LPM
228 Wash	0.4	0.0	130.4			5.67	5.72	06/07/96	08:03 AM	06/07/96	3.0 LPSFH or 1.35 LPM
229 Deaeration	0.9	0.0	131.3			5.72	5.77	06/07/96	08:13 AM	06/07/96	3.0 LPSFH or 1.35 LPM
230 Wash	0.5	0.0	131.8			5.77	5.82	06/07/96	08:23 AM	06/07/96	3.0 LPSFH or 1.35 LPM
231 Flush	0.7	0.0	132.5		131.7	5.82	5.87	06/07/96	08:33 AM	06/07/96	3.0 LPSFH or 1.35 LPM
232 Store	0.7	0.0	133.2		132.3	5.87	5.91	06/07/96	08:43 AM	06/07/96	3.0 LPSFH or 1.35 LPM
233 SIP	1.0	0.0	134.2		133.3	5.91	5.96	06/07/96	08:53 AM	06/07/96	3.0 LPSFH or 1.35 LPM
234 CIP	1.0	0.0	135.2		134.3	5.96	6.00	06/07/96	09:03 AM	06/07/96	3.0 LPSFH or 1.35 LPM
235 Clean Up	1.0	0.0	136.2		135.3	6.00	6.04	06/07/96	09:13 PM	06/07/96	3.0 LPSFH or 1.35 LPM
236 Sub Total	8.7			131.3				06/07/96	09:13 PM	06/07/96	Max FR 1.35 LPM
237 15 A Microfiltration											12.40 SF
238 Set Up	1.0	0.0	131.1			6.02	6.03	06/07/96	10:00 AM	06/07/96	15.0 LPSFH or 3.15 LPM
239 Flush	0.1	0.0	131.2			6.03	6.07	06/07/96	10:05 AM	06/07/96	15.0 LPSFH or 3.15 LPM
240 Prime	0.1	0.0	131.3			6.07	6.11	06/07/96	10:10 AM	06/07/96	15.0 LPSFH or 3.15 LPM
241 Filtration	0.5	0.0	131.8	131.8		6.11	6.16	06/07/96	10:15 AM	06/07/96	15.0 LPSFH or 3.15 LPM
242 Wash	0.0	0.0	131.8			6.16	6.19	06/07/96	10:20 AM	06/07/96	15.0 LPSFH or 3.15 LPM
243 Regenerants	0.0	0.0	131.8			6.19	6.23	06/07/96	10:25 AM	06/07/96	15.0 LPSFH or 3.15 LPM
244 Store	0.1	0.0	131.9		131.9	6.23	6.24	06/07/96	10:30 AM	06/07/96	15.0 LPSFH or 3.15 LPM
245 CIP	1.0	0.0	132.9		132.9	6.24	6.29	06/07/96	10:35 AM	06/07/96	15.0 LPSFH or 3.15 LPM
246 SIP	1.0	0.0	133.9		133.9	6.29	6.34	06/07/96	10:40 AM	06/07/96	15.0 LPSFH or 3.15 LPM
247 Clean Up	1.0	0.0	134.9		134.9	6.34	6.39	06/07/96	10:45 AM	06/07/96	15.0 LPSFH or 3.15 LPM
248 Sub Total	4.9			131.8				06/07/96	10:45 AM	06/07/96	Max FR 1.35 LPM
249 16 A RPLC											60.32 CM DIA.
250 Equilibration	1.1	0.0	131.4			6.43	6.48	06/07/96	10:50 AM	06/07/96	100.0 CMHR or 4.76 LPM
251 Load	0.7	0.0	132.5			6.49	6.52	06/07/96	10:55 AM	06/07/96	100.0 CMHR or 4.76 LPM
252 Wash	1.3	0.0	133.8			6.52	6.58	06/07/96	11:00 AM	06/07/96	100.0 CMHR or 4.76 LPM
253 Elute A	1.3	0.0	135.1			6.58	6.63	06/07/96	11:05 AM	06/07/96	100.0 CMHR or 4.76 LPM
254 Elute B	0.0	0.0	135.1			6.63	6.63	06/07/96	11:10 AM	06/07/96	100.0 CMHR or 4.76 LPM
255 Regenerants	0.2	0.0	135.3			6.63	6.65	06/07/96	11:12 AM	06/07/96	100.0 CMHR or 4.76 LPM
256 Store	0.4	0.0	135.7		135.4	6.65	6.69	06/07/96	11:16 AM	06/07/96	100.0 CMHR or 4.76 LPM
257 CIP	1.0	0.0	136.7		135.9	6.69	6.74	06/07/96	11:21 AM	06/07/96	100.0 CMHR or 4.76 LPM
258 SIP	1.0	0.0	137.7		136.9	6.74	6.79	06/07/96	11:26 AM	06/07/96	100.0 CMHR or 4.76 LPM
259 Clean Up	1.0	0.0	138.7		137.9	6.79	6.84	06/07/96	11:31 AM	06/07/96	100.0 CMHR or 4.76 LPM
260 Sub Total	5.3			135.2				06/07/96	11:31 AM	06/07/96	Max FR 4.76 LPM
261 17 A RPLC											34.76 CM DIA.
262 Equilibration	0.6	0.0	135.6			6.82	6.85	06/07/96	11:36 AM	06/07/96	100.0 CMHR or 4.76 LPM
263 Load	1.1	0.0	136.7			6.85	6.88	06/07/96	11:41 AM	06/07/96	100.0 CMHR or 4.76 LPM
264 Wash	0.8	0.0	137.5			6.88	6.91	06/07/96	11:46 AM	06/07/96	100.0 CMHR or 4.76 LPM
265 Elute A	0.0	0.0	137.5			6.91	6.91	06/07/96	11:51 AM	06/07/96	100.0 CMHR or 4.76 LPM
266 Elute B	0.0	0.0	137.5			6.91	6.91	06/07/96	11:56 AM	06/07/96	100.0 CMHR or 4.76 LPM

FIG. 12F

Process Time Line														
Operation		Duration (Min)		Rel. Time Scale (Min)			Abs. Days			Start		Finish		Calculations
		Calc.	AD	Prep	Exec.	Comp.	Start	End	Date	Time	Date	Time		
355	Regentals	0.1	0.0	0.1	135.0	135.0	5.74	5.75	06:00:00	06:00:00	06:00:00	06:00:00	12.2 L @ 100.0 CHHR or 1.54 LPM	
356	Sieve	0.2	0.0	0.2	135.2	135.2	5.75	5.76	06:00:00	06:00:00	06:00:00	06:00:00	2.4 L @ 100.0 CHHR or 1.51 LPM	
357	CIP	1.0	0.0	1.0	139.2	139.2	6.78	6.80	06:00:00	06:00:00	06:00:00	06:00:00		
358	SIP	1.0	0.0	1.0	140.2	140.2	6.80	6.84	06:00:00	06:00:00	06:00:00	06:00:00		
359	Clean Up	3.0	0.0	1.0	141.2	141.2	6.84	6.85	06:00:00	06:00:00	06:00:00	06:00:00	Max FR 1.50 LPM	
360	Sub Total	6.7		6.7	137.6	137.6							12.20 SF	
18 A. Flow Diagnostics														
361	Set Up	1.0	0.0	1.0	138.5	138.5	5.85	5.89	06:00:00	06:00:00	06:00:00	06:00:00	2.4 L @ 3.0 USFM or 0.81 LPM	
362	Flush	0.7	0.0	0.7	139.2	139.2	5.89	5.92	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
363	Prime	0.7	0.0	0.7	139.9	139.9	5.91	5.94	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
364	Diagnosis	1.0	0.0	1.0	140.9	140.9	6.84	6.88	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
365	Wash	0.0	0.0	0.0	140.9	140.9	6.84	6.88	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
366	Flush	0.3	0.0	0.3	141.2	141.2	6.86	6.90	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
367	Sieve	0.7	0.0	0.7	141.9	141.9	6.88	6.93	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
368	CIP	1.0	0.0	1.0	142.9	142.9	8.93	9.01	06:00:00	06:00:00	06:00:00	06:00:00	Max FR 0.51 LPM	
369	SIP	1.0	0.0	1.0	143.9	143.9	8.93	9.01	06:00:00	06:00:00	06:00:00	06:00:00		
370	Clean Up	1.0	0.0	1.0	144.9	144.9	8.93	9.01	06:00:00	06:00:00	06:00:00	06:00:00		
371	Sub Total	7.3		7.3	133.4	133.4							2.81 CHDZ	
19 A. PIA MPLE														
372	Equilibration	0.5	0.0	0.5	135.5	135.5	5.77	5.79	06:00:00	06:00:00	06:00:00	06:00:00	7.0 L @ 100.0 CHHR or 1.09 LPM	
373	Load	0.2	0.0	0.2	135.7	135.7	5.78	5.79	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
374	Wash	0.8	0.0	0.8	136.7	136.7	6.83	6.85	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
375	Exhaust A	0.0	0.0	0.0	140.3	140.3	6.83	6.85	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
376	Exhaust B	0.0	0.0	0.0	140.3	140.3	6.83	6.85	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
377	Regentals	0.1	0.0	0.1	140.3	140.3	6.83	6.85	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
378	Sieve	0.2	0.0	0.2	140.7	140.7	6.86	6.88	06:00:00	06:00:00	06:00:00	06:00:00	3.0 USFM or 0.81 LPM	
379	CIP	1.0	0.0	1.0	141.7	141.7	8.84	8.90	06:00:00	06:00:00	06:00:00	06:00:00	Max FR 1.09 LPM	
380	SIP	1.0	0.0	1.0	142.7	142.7	8.84	8.90	06:00:00	06:00:00	06:00:00	06:00:00		
381	Clean Up	1.0	0.0	1.0	143.7	143.7	8.84	8.90	06:00:00	06:00:00	06:00:00	06:00:00	Max FR 1.09 LPM	
382	Sub Total	5.4		5.4	140.3	140.3							2.43 SF	
20 A. Flow Diagnostics														
383	Set Up	0.0	0.0	0.0	138.0	138.0	5.79	5.79	06:00:00	06:00:00	06:00:00	06:00:00	4.9 L @ 3.0 USFM or 0.12 LPM	
384	Flush	0.7	0.0	0.7	138.7	138.7	5.83	5.85	06:00:00	06:00:00	06:00:00	06:00:00	4.9 L @ 3.0 USFM or 0.12 LPM	
385	Prime	2.0	0.0	2.0	140.3	140.3	6.83	6.85	06:00:00	06:00:00	06:00:00	06:00:00	4.9 L @ 3.0 USFM or 0.12 LPM	
386	Diagnosis	0.0	0.0	0.0	142.3	142.3	6.83	6.85	06:00:00	06:00:00	06:00:00	06:00:00	4.9 L @ 3.0 USFM or 0.12 LPM	
387	Wash	0.0	0.0	0.0	142.3	142.3	6.83	6.85	06:00:00	06:00:00	06:00:00	06:00:00	4.9 L @ 3.0 USFM or 0.12 LPM	
388	Flush	0.3	0.0	0.3	142.7	142.7	6.84	6.87	06:00:00	06:00:00	06:00:00	06:00:00	4.9 L @ 3.0 USFM or 0.12 LPM	
389	Sieve	0.7	0.0	0.7	143.3	143.3	6.87	6.87	06:00:00	06:00:00	06:00:00	06:00:00	4.9 L @ 3.0 USFM or 0.12 LPM	
390	CIP	0.0	0.0	0.0	143.3	143.3	6.87	6.87	06:00:00	06:00:00	06:00:00	06:00:00	4.9 L @ 3.0 USFM or 0.12 LPM	
391	SIP	0.0	0.0	0.0	143.3	143.3	6.87	6.87	06:00:00	06:00:00	06:00:00	06:00:00	4.9 L @ 3.0 USFM or 0.12 LPM	
392	Clean Up	0.0	0.0	0.0	144.3	144.3	6.87	6.87	06:00:00	06:00:00	06:00:00	06:00:00	Max FR 0.12 LPM	
393	Sub Total	4.3		4.3	142.3	142.3							2.83 CHDZ	
21 A. PIA MPLE														
394	Equilibration	0.5	0.0	0.5	142.0	142.0	5.89	5.91	06:00:00	06:00:00	06:00:00	06:00:00	100.0 CHHR or 0.91 LPM	
395	Load	0.1	0.0	0.1	142.4	142.4	5.93	5.94	06:00:00	06:00:00	06:00:00	06:00:00	60.0 CHHR or 0.45 LPM	
396	Wash	0.6	0.0	0.6	143.0	143.0	5.94	5.96	06:00:00	06:00:00	06:00:00	06:00:00	60.0 CHHR or 0.45 LPM	
397	Exhaust A	0.0	0.0	0.0	143.6	143.6	5.94	5.96	06:00:00	06:00:00	06:00:00	06:00:00	60.0 CHHR or 0.45 LPM	
398	Exhaust B	0.0	0.0	0.0	143.6	143.6	5.94	5.96	06:00:00	06:00:00	06:00:00	06:00:00	30.0 CHHR or 0.27 LPM	
399	Regentals	0.1	0.0	0.1	143.7	143.7	5.99	6.00	06:00:00	06:00:00	06:00:00	06:00:00	100.0 CHHR or 0.91 LPM	
400	Sieve	0.2	0.0	0.2	143.9	143.9	6.00	6.00	06:00:00	06:00:00	06:00:00	06:00:00	100.0 CHHR or 0.91 LPM	
401	CIP	0.0	0.0	0.0	143.9	143.9	6.00	6.00	06:00:00	06:00:00	06:00:00	06:00:00		
402	SIP	0.0	0.0	0.0	143.9	143.9	6.00	6.00	06:00:00	06:00:00	06:00:00	06:00:00		
403	Clean Up	0.0	0.0	0.0	143.9	143.9	6.00	6.00	06:00:00	06:00:00	06:00:00	06:00:00	Max FR 0.91 LPM	
404	Sub Total	0.0		0.0	143.6	143.6								

FIG. 12 G

Line	Operation	Duration (Hr)		Risk Time Scale (Hr)		Abs. Dose		Start		Finish		Calculations
		Crit.	AD	Prep	Exec.	Compd.	Start	End	Date	Time	Date	Time
416	Clean Up	1.0	0.0		13.5		06/03/98	08:00 AM	06/03/98	08:00 AM		
417	Sub Total	2.1		14.0			06/03/98	08:00 AM	06/03/98	11:54 PM	06/03/98	12:54 AM
418	22 A. Sterile Filtration											Max FR 0.91 LPM
419	Set Up	0.5	0.0	132.6			06/03/98	01:00 AM	06/03/98	01:00 AM	06/03/98	01:09 PM
420	Filtration	0.5	0.0		144.1		06/03/98	11:20 PM	06/03/98	06:00 PM	06/03/98	12:00 AM
421	Storage	0.5	0.0			144.0	06/03/98	01:00 AM	06/03/98	12:00 AM	06/03/98	12:30 AM
422	CIP	0.0	0.0			144.0	06/03/98	01:00 AM	06/03/98	12:30 AM	06/03/98	12:30 AM
423	SIP	0.0	0.0			144.0	06/03/98	01:00 AM	06/03/98	12:30 AM	06/03/98	12:30 AM
424	Clean Up	1.0	0.0		144.1		06/03/98	12:30 AM	06/03/98	12:30 AM	06/03/98	01:12 AM
425	Sub Total	1.5		144.1								Max FR 0.07 LPM

FIG. 12H

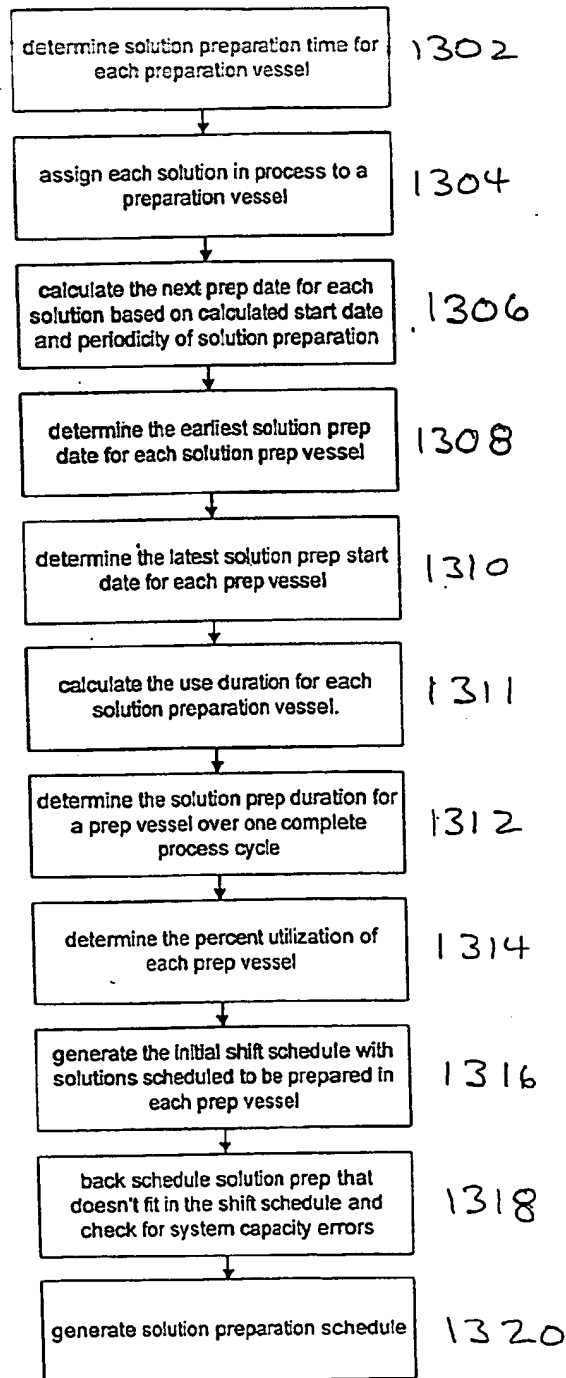
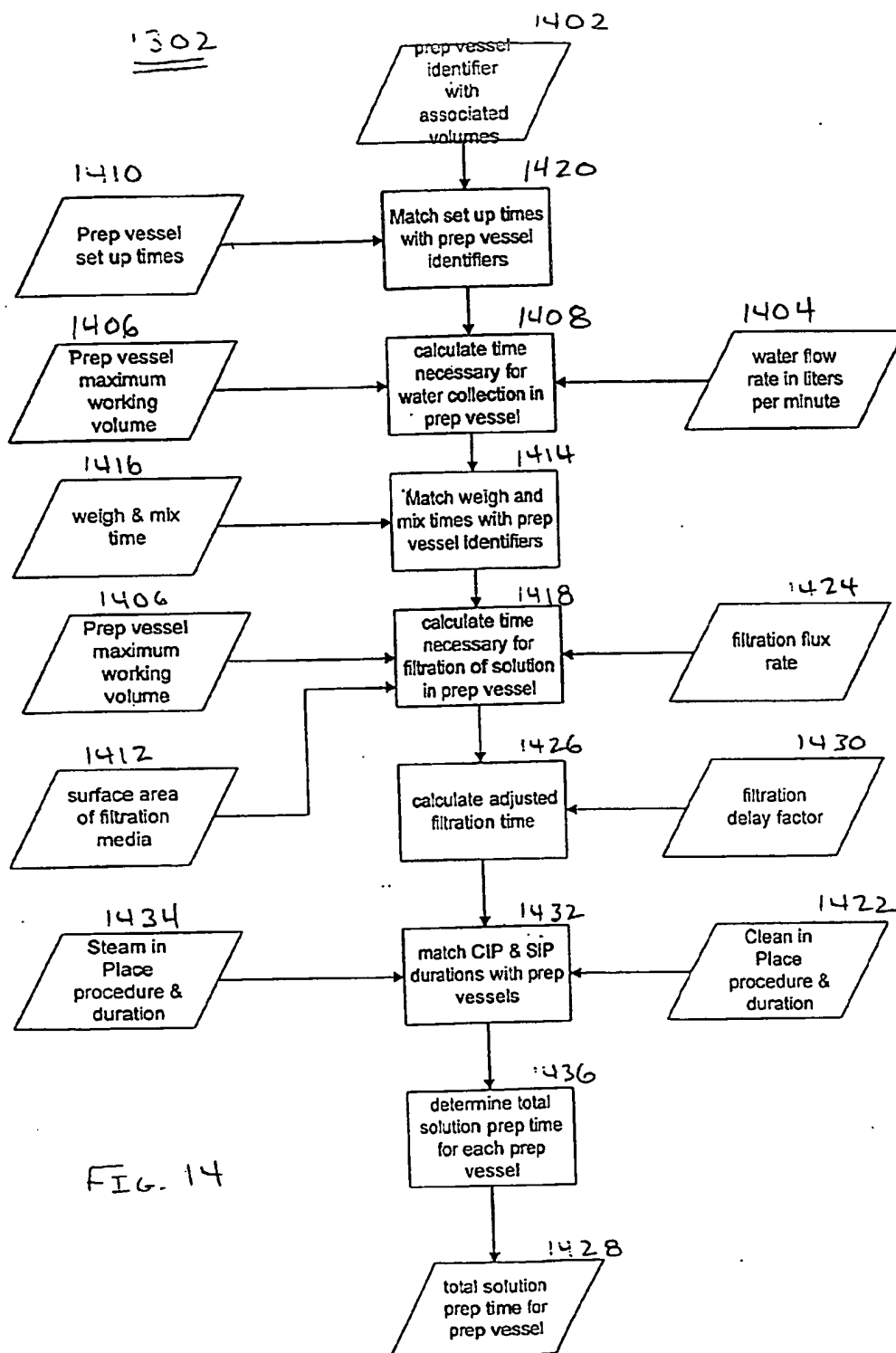


FIG. 13



Batch Tank		Batch Tank		Set Up Min.	Water Collect.		Weight/ Mix Min.	Ultrafiltration/Microfiltration				CIP		Total		Perc. Util.		
No.	Min. LWV	No.	Min. LWV		Max. LWV	LPM		Min.	SF	USF/HR	Min.	Delay Factor	Adj. Min.	Cycle	Min.		SIP	Min.
101	0.5	101	0.5	1	10	1	15	0.5	26	4.8	1.2	5.76			31.78	0.6	2%	
102	1	102	1	2	10	1	15	1	26	4.8	1.2	6.78			31.78	0.5	1.1	
103	2	103	2	4	20	2	30	1	25	9.6	1.2	11.52			63.52	1.1	4%	
104	4	104	4	10	20	10	30	2	25	12	1.2	14.4			65.4	1.1		
105	10	105	10	20	20	10	30	2	25	24	1.2	28.8			80.8	1.3		
106	20	106	20	50	20	10	30	10	25	12	1.2	14.4	CIP-1	60	40	109.4	1.8	3%
107	60	107	60	100	20	10	30	10	25	24	1.2	28.8	CIP-1	60	40	128.6	2.1	8%
108	100	108	100	250	0.5	50	30	30	25	20	1.2	24	CIP-1	60	40	99.5	1.7	18%
109	250	109	250	500	0.5	50	30	30	25	40	1.2	48	CIP-1	60	40	128.5	2.1	11%
110	500	110	500	1,500	1	50	30	60	25	60	1.2	72	CIP-1	60	40	173	2.9	10%
111	1500	111	1500	3,000	1	50	30	60	25	120	1.2	144	CIP-1	60	40	276	4.6	16%

1402

1406

1410

1404

1412

1424

1506

1428

1434

502

FIG. 12

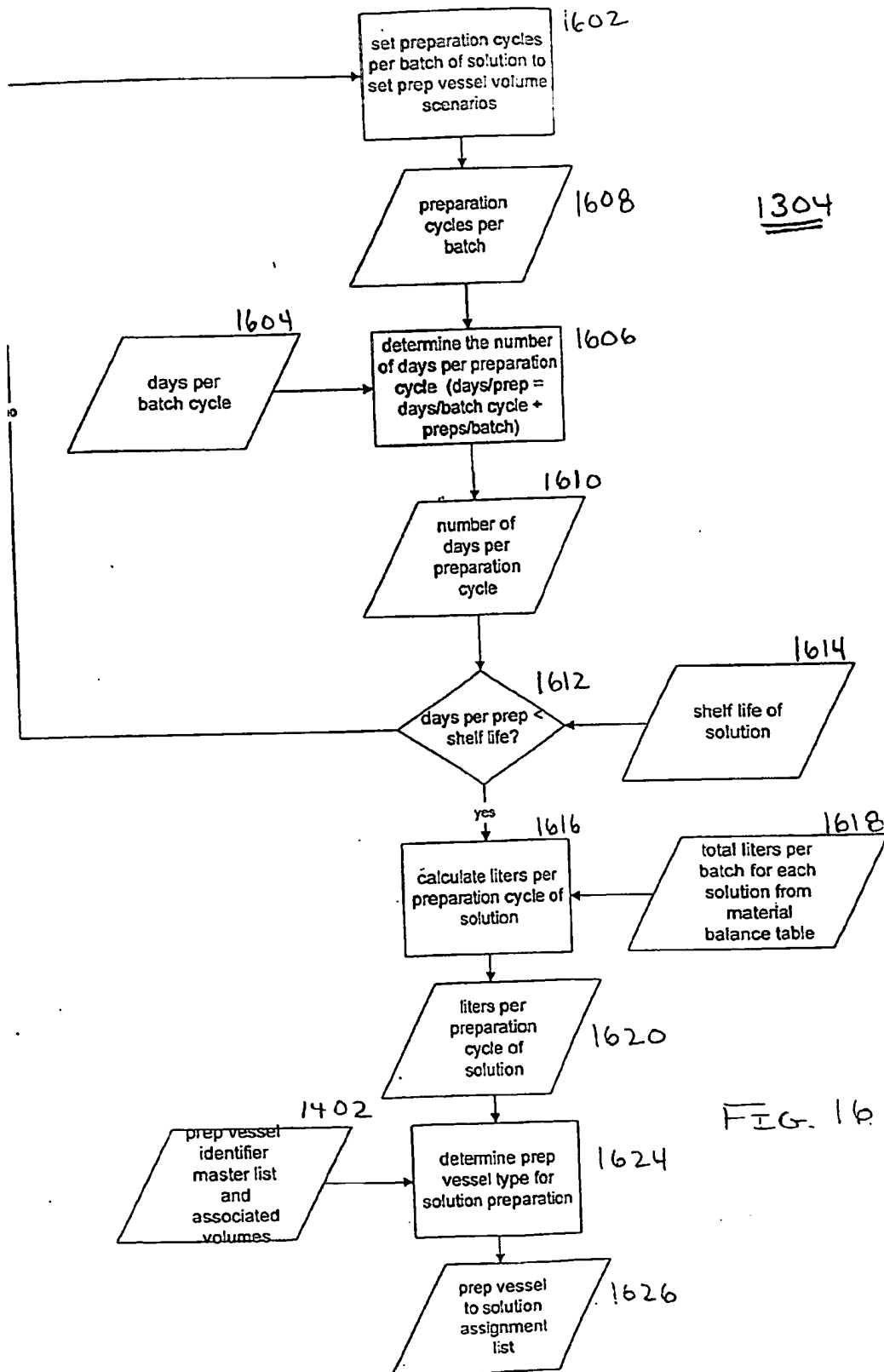


FIG. 16

Solution Prep Campaign Format

1626

Soln. ID	Storage Cond.		Soln. Prep Format			Solution Prep Cycles		Liters/ Prop	Days/ Bal. Cy.	Days/ Prop	Shelf Days	Shelf Check	101		102		103		104		105		106		107	
	RT	4C	XP	MOD	DOD	BIA	Liters/ Batch						Preps/ Batch	0.6	1	2	4	10	20	40	60	80	100			
1 S-0101	X			0	X	0	1,666.50	1	7	7	56	OK	102													
2 S-0102	X			0	X	0	1.65	1	7	7	180	OK	102													
3 S-0103	X			0	X	0	1.65	1	7	7	180	OK														
4 S-0104	X			0	X	0	8.25	1	7	7	56	OK							104	104						
5 S-0105	X			0	X	0	8.25	1	7	7	56	OK														
6 S-0106	X			0	X	0	560.61	1	7	7	56	OK														
7 S-0107	X			0	X	0	125.93	1	7	7	56	OK														
8 S-0108	X			0	X	0	177.41	1	7	7	56	OK														
9 S-0109	X			0	X	0	22.18	1	7	7	56	OK														
10 S-0110	X			0	X	0	56.52	1	7	7	56	OK														
11 S-0111	X			0	X	0	113.03	1	7	7	56	OK														
12 S-0112	X			0	X	0	1,612.45	1	7	7	56	OK														
13 S-0113	X			0	X	0	574.10	1	7	7	56	OK														
14 S-0114	X			0	X	0	248.83	1	7	7	56	OK														
15 S-0115	X			0	X	0	497.65	1	7	7	56	OK														
16 S-0116	X			0	X	0	109.80	1	7	7	56	OK														
17 S-0117	X			0	X	0	497.65	1	7	7	56	OK														
18 S-0118	X			0	X	0	292.78	1	7	7	56	OK														
19 S-0119	X			0	X	0	109.80	1	7	7	56	OK														
20 S-0120	X			0	X	0	62.58	1	7	7	56	OK														
21 S-0121	X			0	X	0	0.00	1	7	7	56	OK														
22 S-0122	X			0	X	0	0.00	1	7	7	56	OK														

1704 1610 1608 1620 1604 1610 1614 1706

FIG. 17

Solution Prep Campaign Format

1626

Soln. ID	Tank Assignment				Solution Prep Schedule							Tank Fill				
	100 260	108 250 600	109 500 1600	111 1500 3000	Initial Assign.	Final Assign.	Required By	Back Days	Avail. By	Hold Days	Init. Start	Float Days	Final Start	Next Prep	Prep. Hrs.	101
1 S-0101				111	111	111	06/03/96	1	05/31/96	2	05/29/96	0	05/29/96	06/05/96	4	
2 S-0102				111	102	102	06/05/96	1	06/04/96	2	05/31/96	0	06/01/96	06/07/96	4	
3 S-0103				111	102	102	06/05/96	1	06/04/96	2	05/31/96	0	06/01/96	06/07/96	4	
4 S-0104				111	104	104	06/05/96	1	06/04/96	2	05/31/96	0	06/01/96	06/07/96	4	
5 S-0105				111	104	104	06/05/96	1	06/04/96	2	05/31/96	0	06/01/96	06/07/96	4	
6 S-0106				111	110	110	06/05/96	1	06/04/96	2	06/04/96	0	06/04/96	06/11/96	4	
7 S-0107				111	108	108	06/11/96	1	06/10/96	2	06/07/96	0	06/07/96	06/14/96	4	
8 S-0108				111	108	108	06/11/96	1	06/10/96	2	06/07/96	0	06/07/96	06/14/96	4	
9 S-0109				111	107	107	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
10 S-0110				111	108	108	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
11 S-0111				111	108	108	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
12 S-0112				111	111	111	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
13 S-0113				111	110	110	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
14 S-0114				111	108	108	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
15 S-0115				111	109	109	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
16 S-0116				111	108	108	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
17 S-0117				111	109	109	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
18 S-0118				111	109	109	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
19 S-0119				111	108	108	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
20 S-0120				111	107	107	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
21 S-0121				111	0	0	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	
22 S-0122				111	0	0	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96	4	

1722

1726

1728

1724

06/03/96

06/12/96

0

Min

Max

Sat

Sun

Min.

Min

05/29/96

06/14/96

M/h. 05/29/96 08/14/96

Min Max Sat Sun
06/03/96 06/12/96 0 0

1722 1726 1728 1724

Fig 18

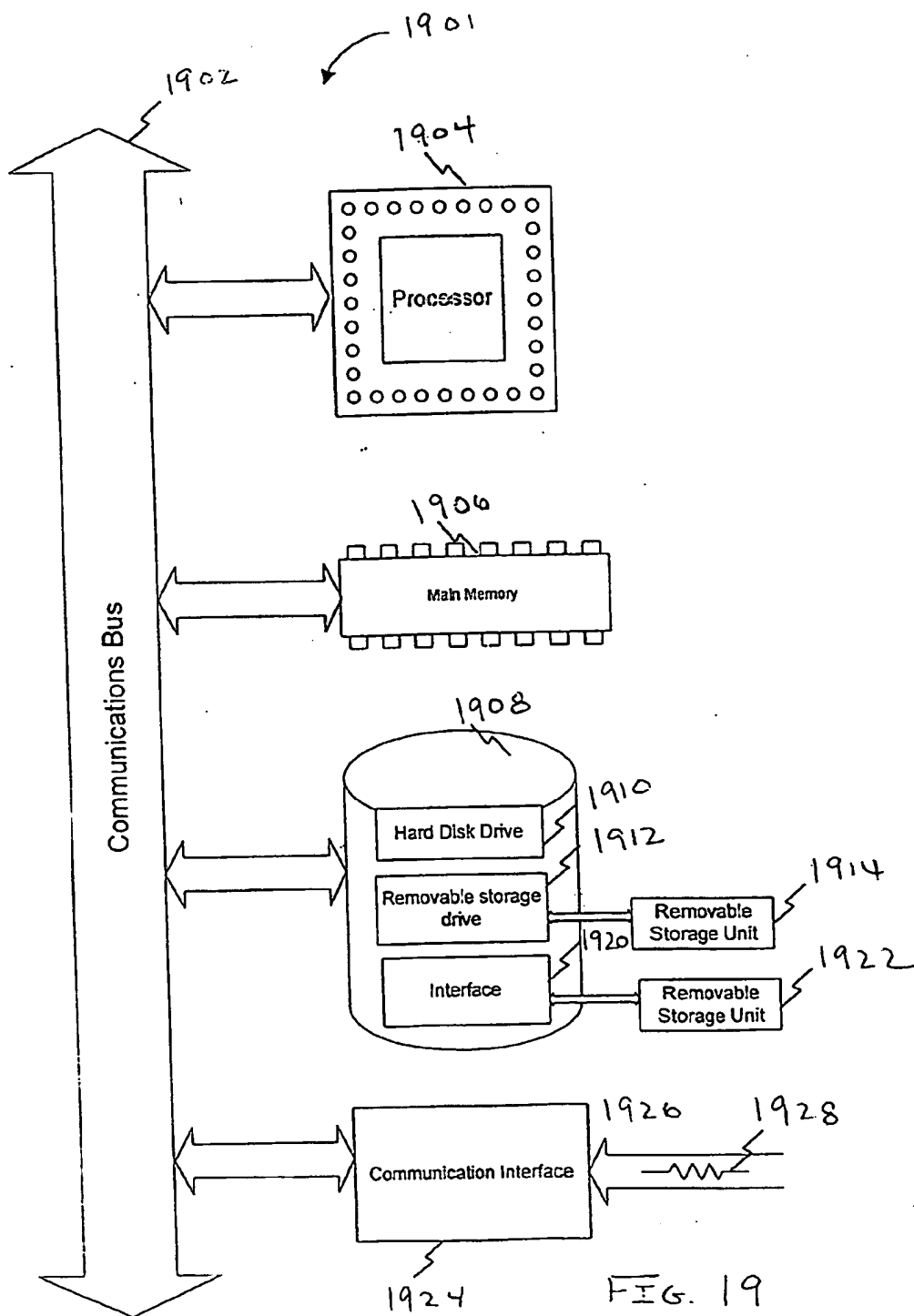
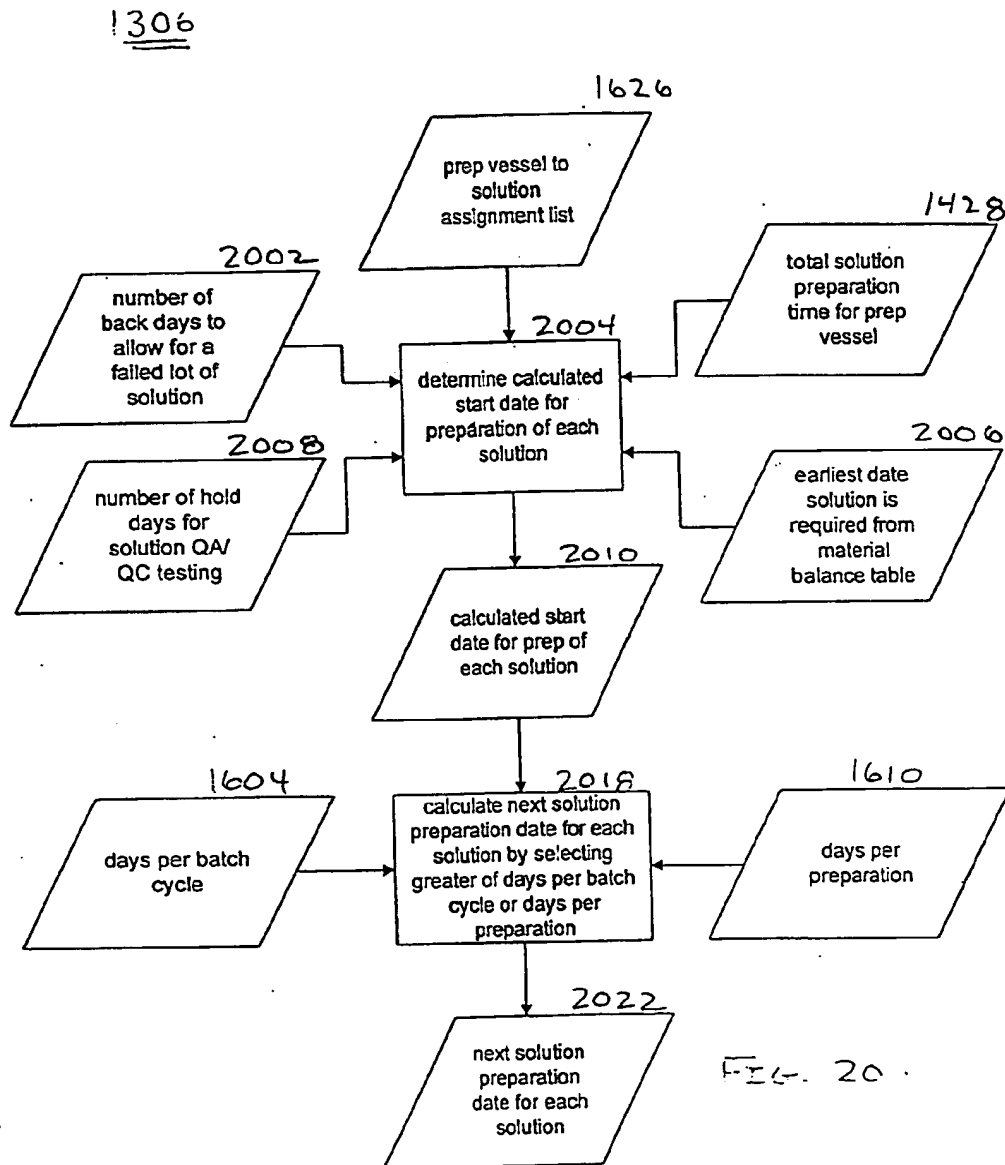


FIG. 19



	Category/Assay	Code	Man Hour			Disp. Material
			Set Up	Per Sample	Clean Up	
1	Environmental					
2	Temperature	E-1	0.5	0.1	0.5	
3	Humidity	E-2	0.5	0.1	0.5	
4	Particle Count	E-3	0.5	0.2	0.5	
5						
6	Analytical					
7	Visual					
8	Certificate of Analysis	AV-1	0.25	0.2	0.5	
9	Appearance	AV-2	0.25	0.05	0.25	
10	Chemical					
11	Solubility	AC-1	0.5	0.1	0.5	
12	pH	AC-2	0.25	0.05	0.25	
13	Osmolality	AC-3	0.25	0.1	0.25	
14	Water Content (by Karl Fischer)	AC-4	0.5	0.2	0.5	
15	Key Element Analysis (by ICP Atomic Adsorption Spectroscopy)	AC-5	1	0.25	1	
16	GC/Mass Spec	AC-6	1	0.25	1	
17	Biochemical					
18	DNA					
19	DNA Fluorochrome Stain	AB-1	0.5	0.1	0.5	
20	Protein					
21	Hemoglobin	AB-2	0.5	0.1	0.5	
22	Electrophoretic Profiles by SDS-PAGE	AB-3	1	0.2	1	
23	A280	AB-4	0.25	0.1	0.25	
24	Bradford Assay	AB-5	0.5	0.1	0.5	
25	Amino Acid Analysis by HPLC	AB-6	1	0.25	1	
26	Endotoxin		0.5	0.1	0.5	
27	Gel Clot LAL	AB-7				
28	Immunological					
29	ELISA	AI-1	1	0.1	1	
30	Western Blots	AI-2	1.5	0.2	1.5	
31	Activity					
32	Chromagenic Substrate Assays	AA-1	1	0.1	1	
33						
34	In Vitro Biological					
35	Microbiological					
36	Mycoplasma (Barile Method)	VB-1	0.5	0.2	0.5	
37	Bacteriophage (Screened)	VB-2	0.5	0.2	0.5	
38	Cell Passage Test	VB-3	0.5	0.2	0.5	
39	Adventitious viral Agents	VB-4	1	0.2	1	
40	CPE		2	0.2	1	
41	BVD	VB-5	2	0.2	1	
42	P13	VB-6	2	0.2	1	
43	IBR	VB-7	2	0.2	1	
44	Virus Neutralization Titers (9CFR)	VB-8	2	0.2	1	
45	BVD	VB-9	2	0.2	1	
46	P13	VB-10	2	0.2	1	
47	IBR	VB-11	2	0.2	1	
48	Trinitated Thymidine Uptake in Mouse Cells	VB-12	2	0.2	1	
49	General Safety Test (Guinea Pigs)	VB-13	1	0.2	1	
50						
51						

FIG. 21

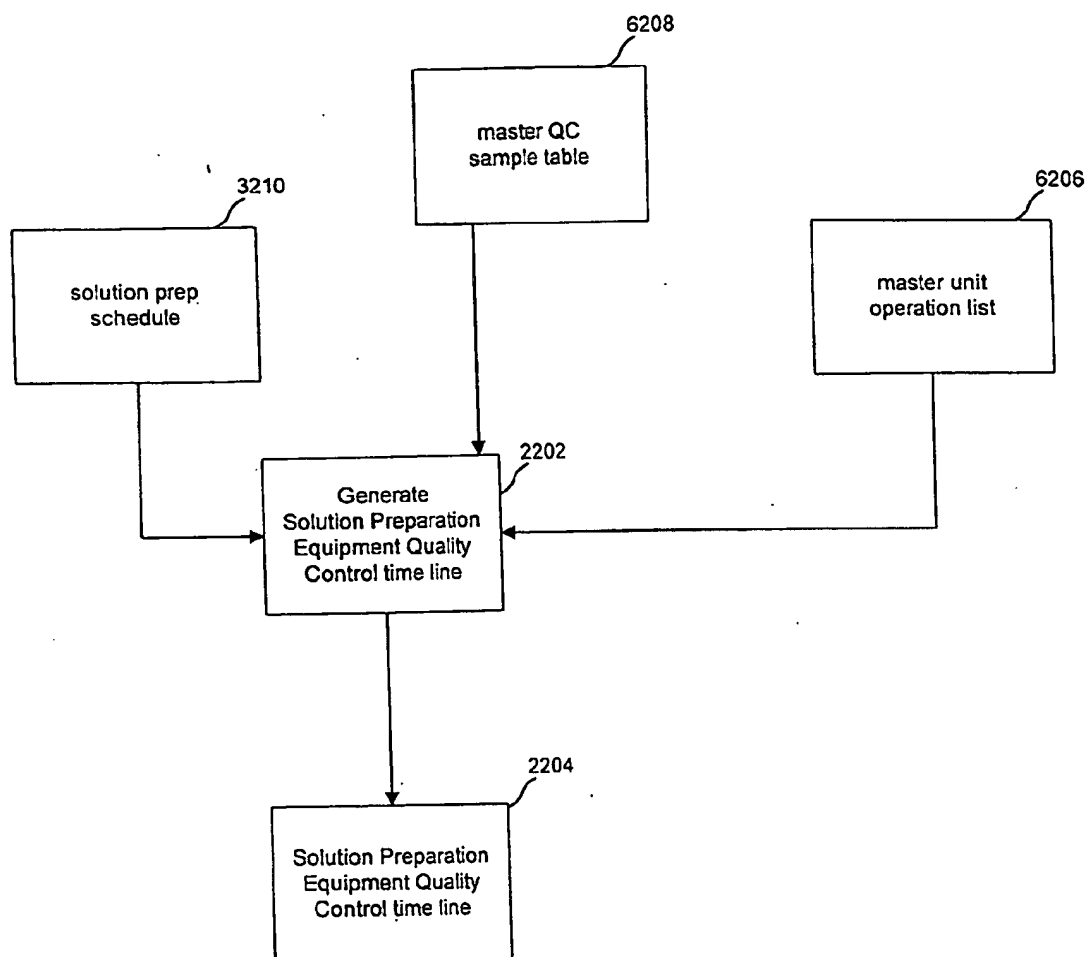
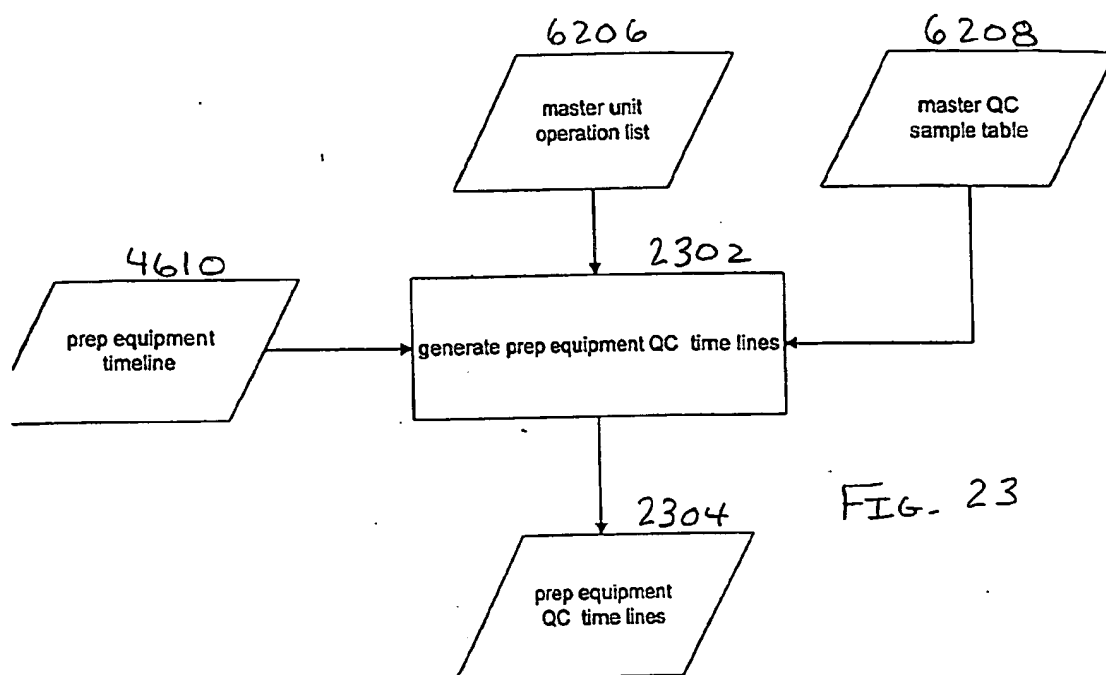
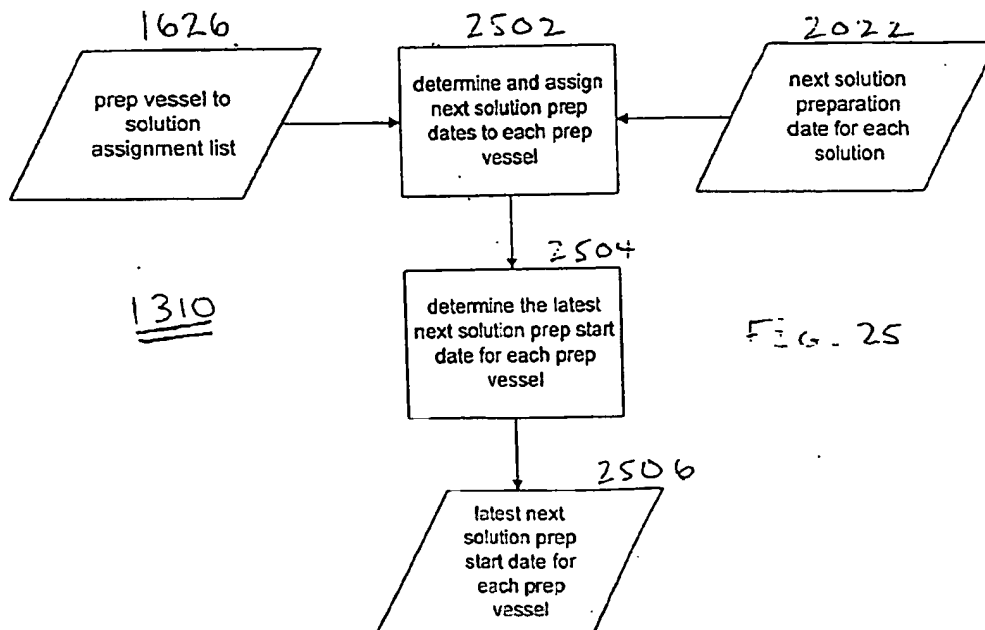
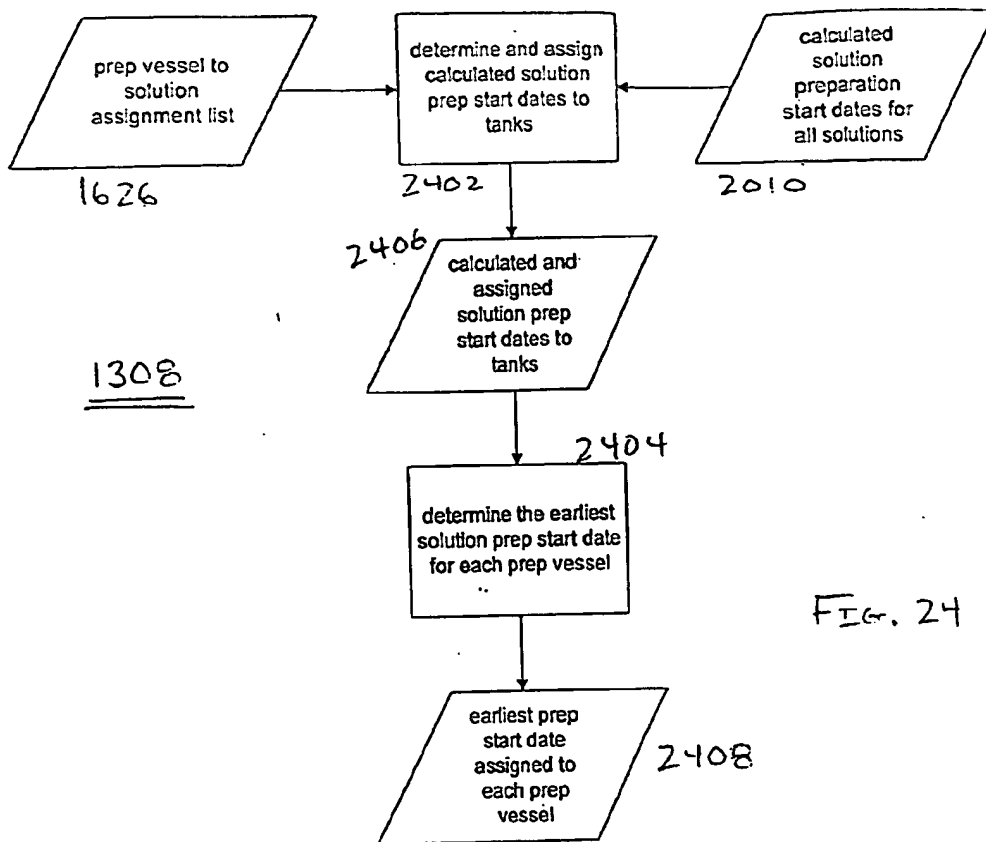
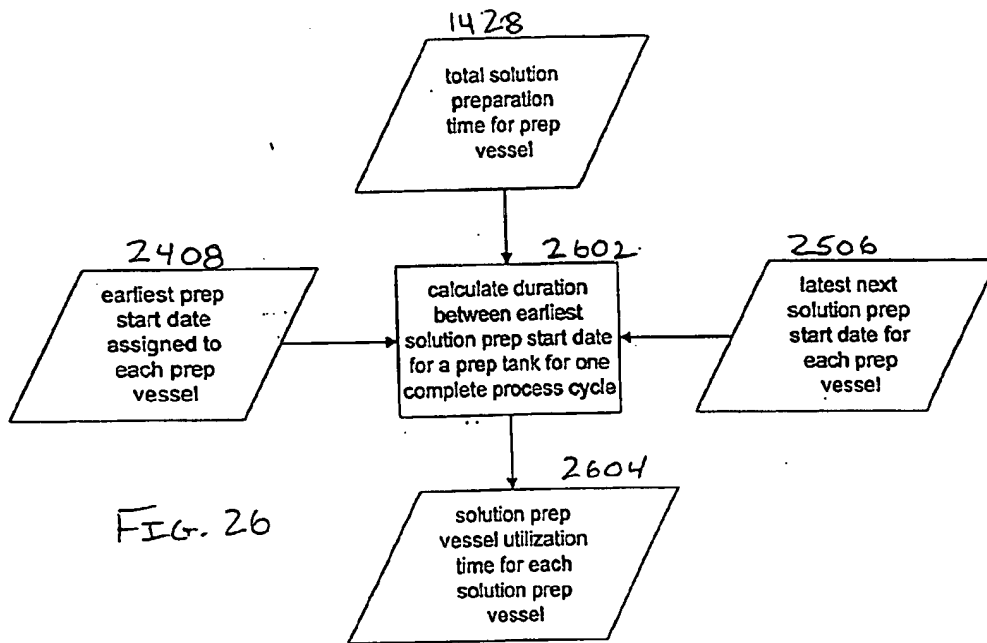
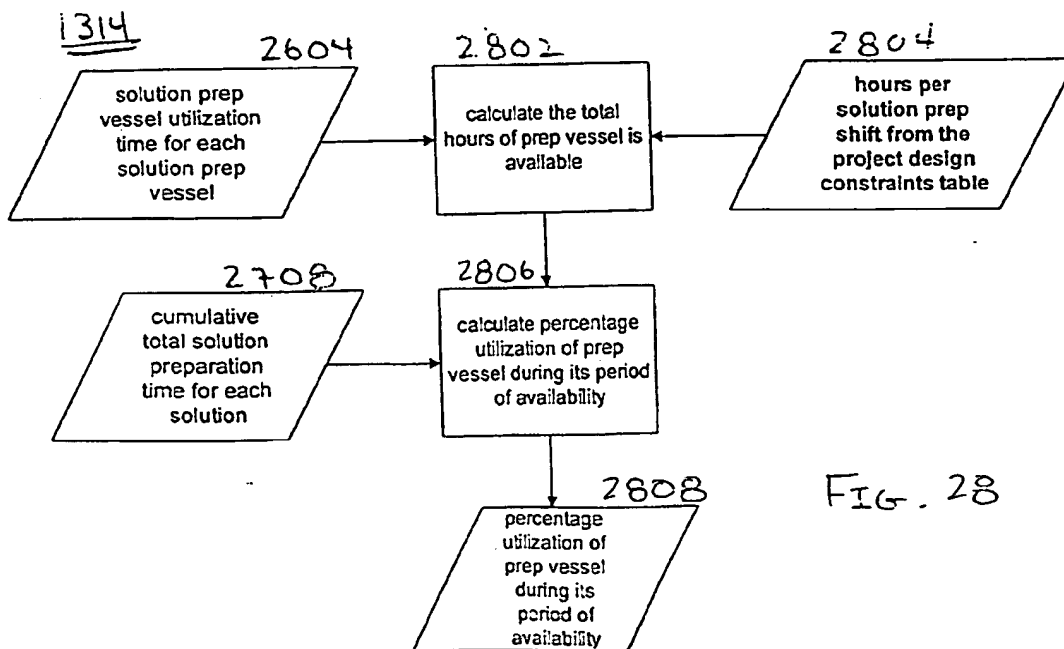
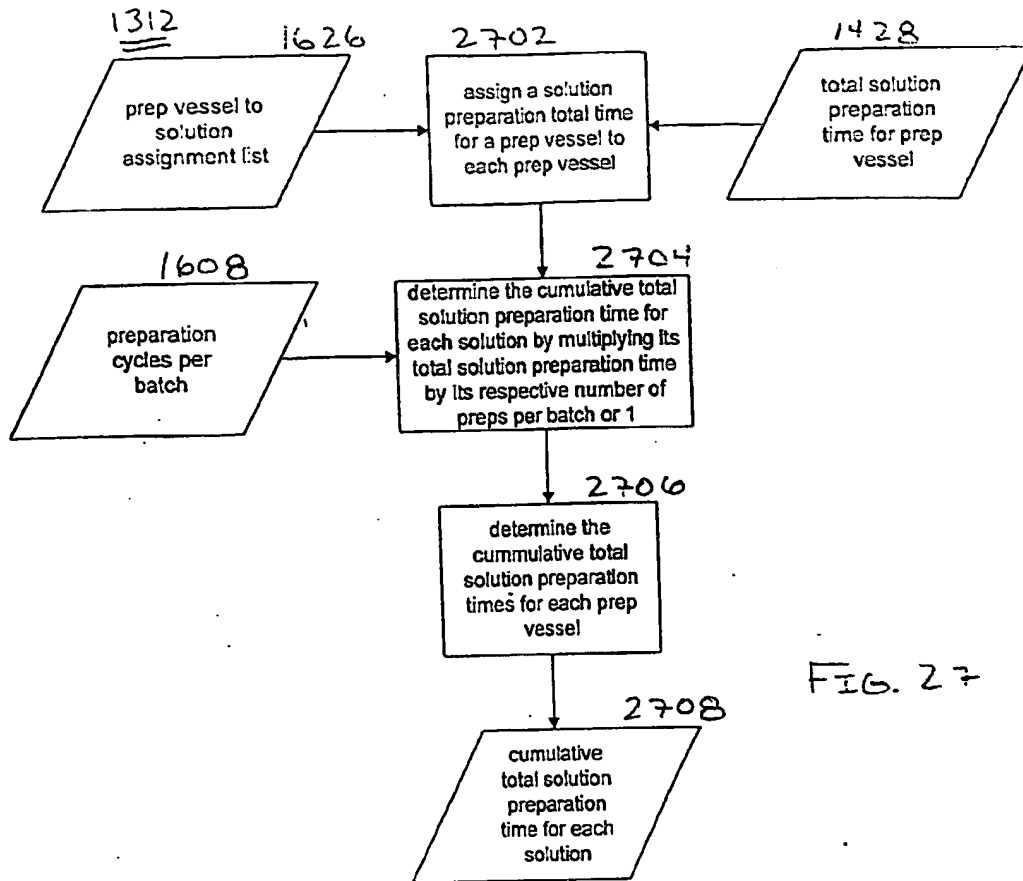


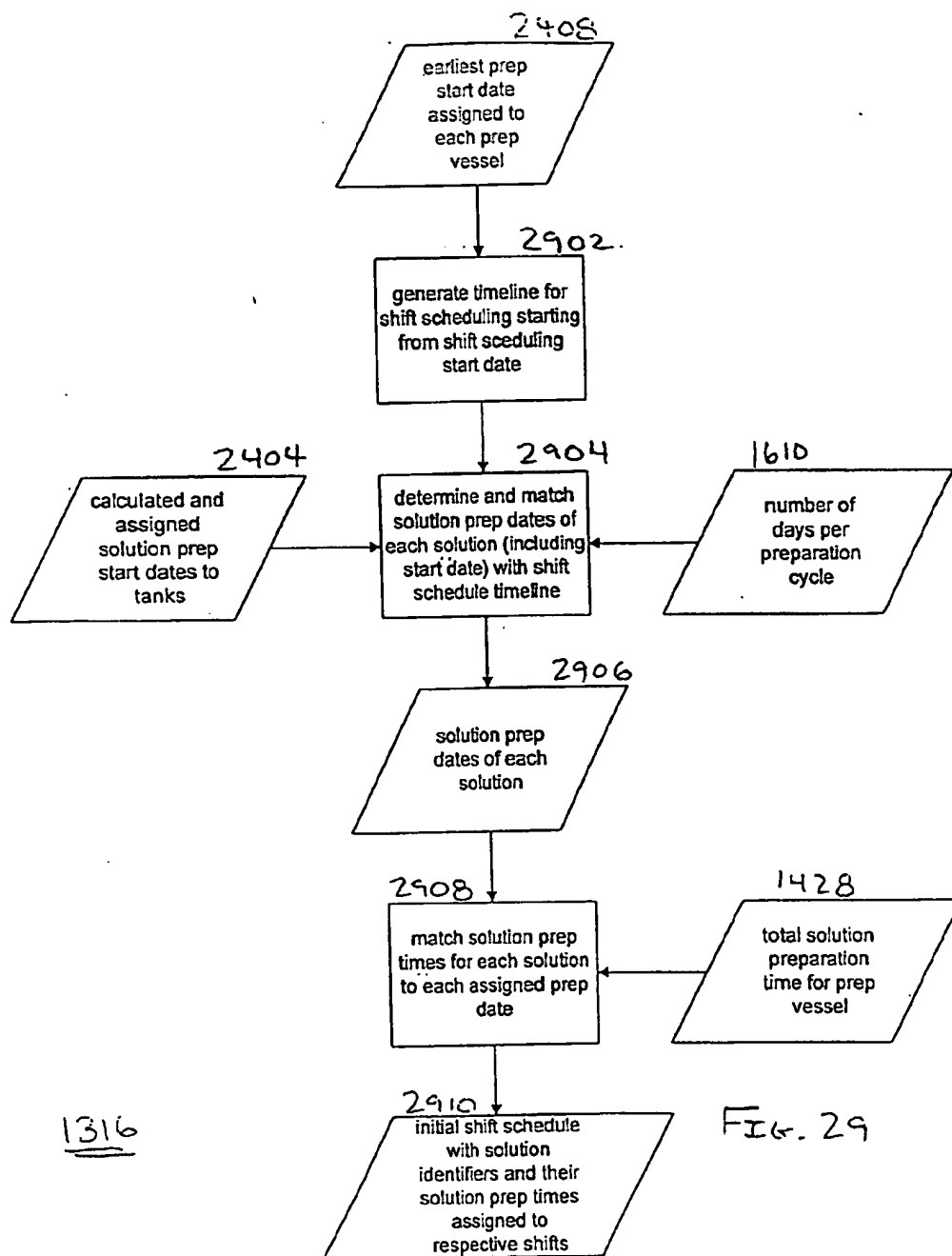
FIG. 22

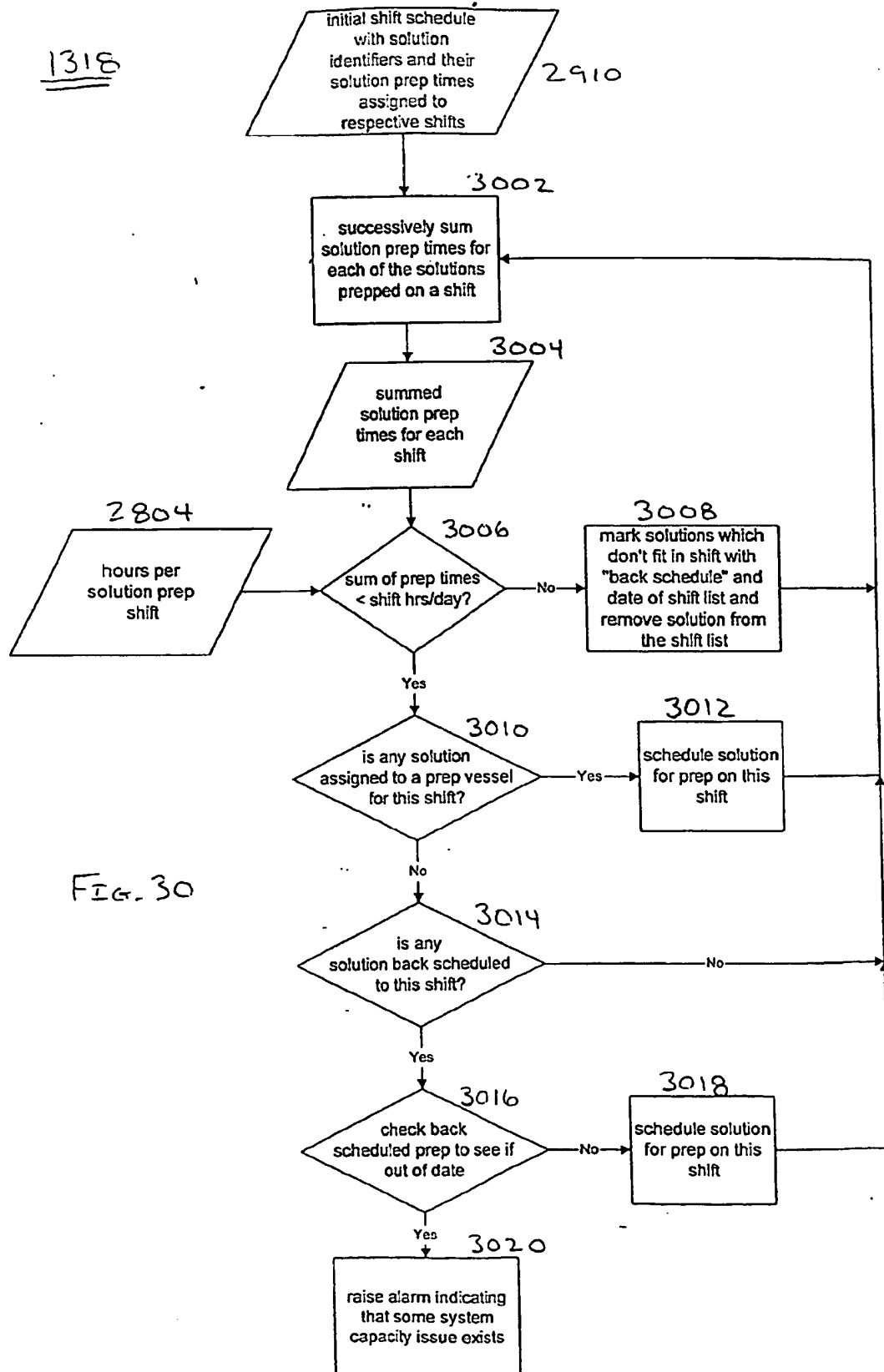




1312







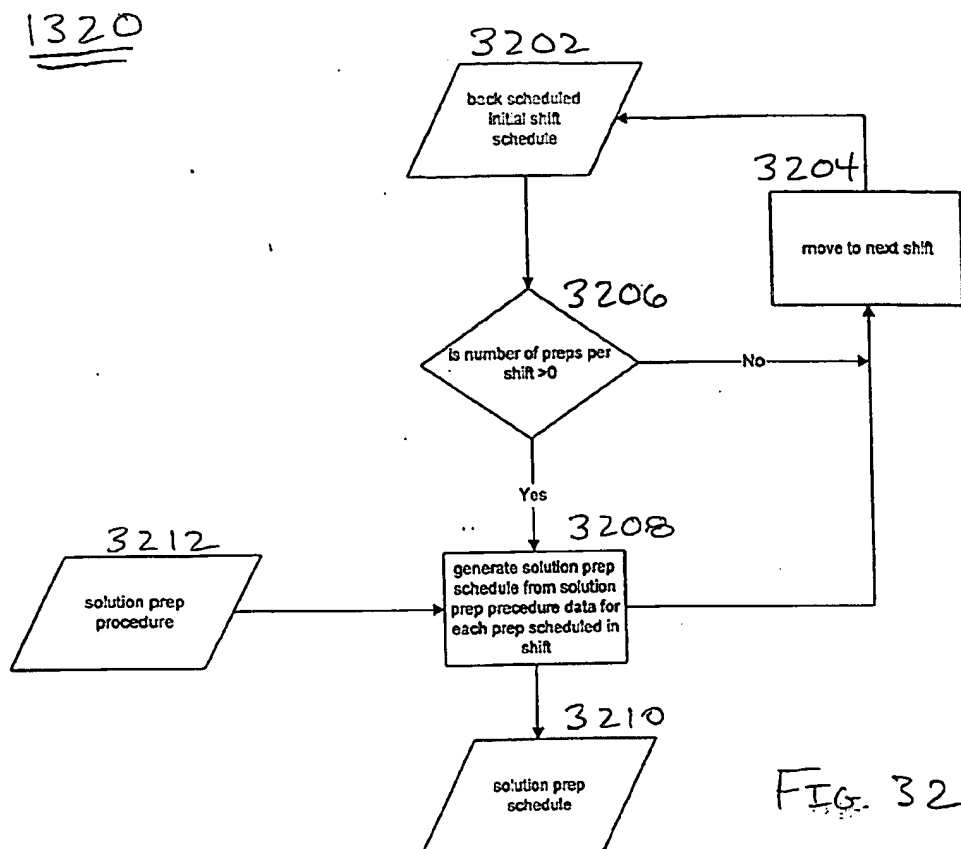
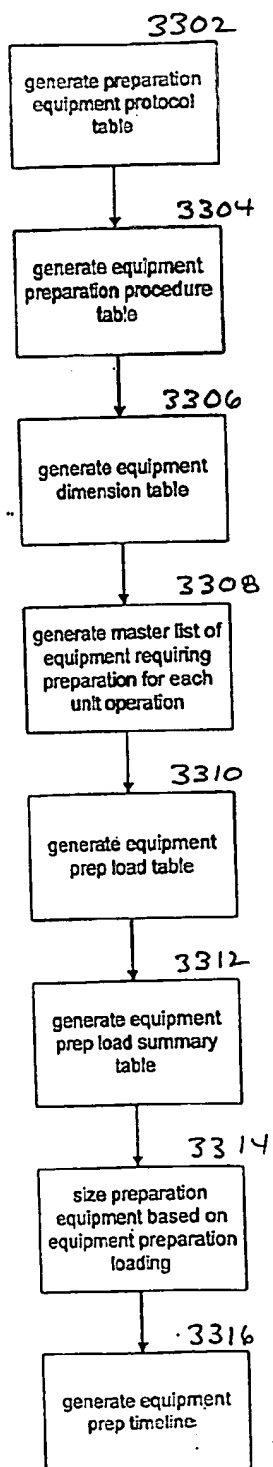
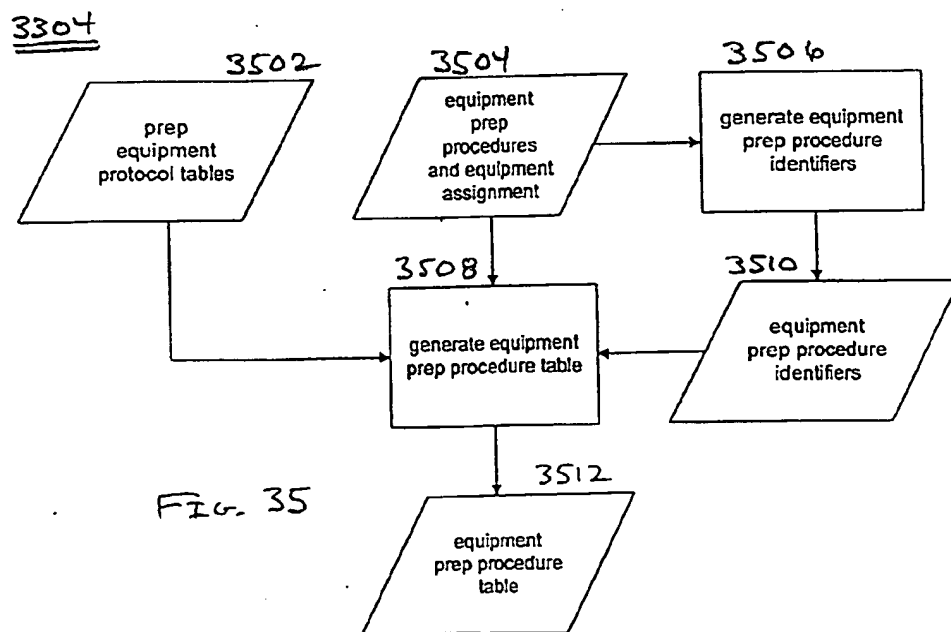
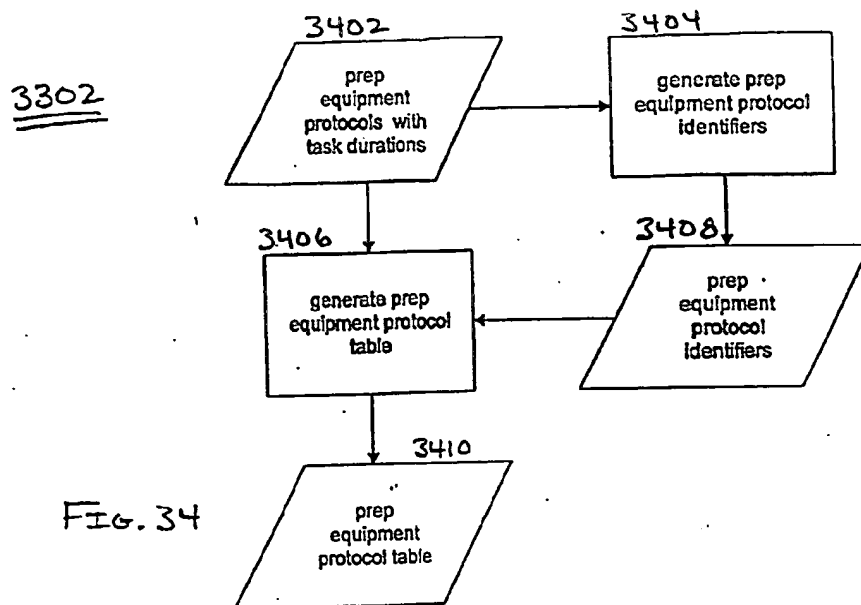


FIG. 32

FIG. 33





Prep Equipment Protocol - Bench Sink

3408

3602

3604

Prep Equipment Protocol - Bench Wash

	Cyclic Code	Minutes/Cycle										Total
		Load	Pre Wash Rinse		Detergent Wash			Post Wash Rinse		Final Rinse	Hold/Dry	
			NPHW	NPCW	Minutes	Reagent	Gm/CF	NPHW	NPCW			
1	B8-1	5	2	2	5	Alconox	0.5	2	2	2		20
2	B8-2	5	2	2	5	Alconox	0.6	2	2	2		20
3	B8-3	5	2	2	5	Alconox	0.6	2	2	2		20
4	B8-4	5	2	2	5	Alconox	0.5	2	2	2		20
5	B8-5	5	2	2	5	Alconox	0.5	2	2	2		20

FIG. 36A

Prep Equipment Protocol - Wash Station

3408

Protocol	Minutes/Cycle										Total
	Cycle Code	Load	Pre Wash Rinse		Detergent Wash			Post Wash Rinse		Final Rinse	
			NPHW	NPCW	Minutes	Reagent	Gm/CF	NPHW	NPCW		
1	WS-1	5	2	2	5	Alconox	0.5	2	2	2	15
2	WS-2	5	2	2	5	Alconox	0.5	2	2	2	15
3	WS-3	5	2	2	5	Alconox	0.5	2	2	2	15
4	WS-4	5	2	2	5	Alconox	0.5	2	2	2	15
5	WS-5	5	2	2	5	Alconox	0.5	2	2	2	15

FIG. 36B

Prep Equipment Protocol - Glassware Washer

	Cycle Code	Minutes/Cycle										Total
		Load	Pre Wash Rinse		Detergent Wash			Post Wash Rinse		Final Rinse	Unload	
			NPHW	NPCW	Minutes	Reagent	Gm/CF	NPHW	NPCW			
1	GW-1	15	2	2	5	Alconox	0.5	2	2	2	10	40
2	GW-2	15	2	2	5	Alconox	0.5	2	2	2	10	40
3	GW-3	15	2	2	5	Alconox	0.5	2	2	2	10	40
4	GW-4	15	2	2	5	Alconox	0.5	2	2	2	10	40
5	GW-5	15	2	2	5	Alconox	0.5	2	2	2	10	40

FIG. 36C

Prep Equipment Protocol - Glassware Dryer

3408

	Cycle Code	Load	Heat Up Minutes	Dry		Cool Minutes	Unload	Total
				Temp (C)	Minutes			
1	DO-1	10	30	250	40	30	10	120
2	DO-2	10	30	250	25	30	10	105
3	DO-3	10	30	250	25	30	10	105
4	DO-4	10	30	250	25	30	10	105
5	DO-5	10	30	250	25	30	10	105

3618

3620

3622

3624

3626

3628

FIG. 36D

Prep Equipment Protocol - Carboy Washer

3408

Cycle Code	Minutes/Cycle											Total
	Load	Pre Wash Rinse		Detergent			Post Wash Rinse		Final Rinse	Unload		
		NPHW	NPCW	Minutes	Reagent	Gm/CF	NPHW	NPCW				
1 CW-1	15	2	2	5	Alconox	0.5	2	2	2	15	16	
2 CW-2	15	2	2	5	Alconox	0.5	2	2	2	15	15	
3 CW-3	15	2	2	5	Alconox	0.5	2	2	2	15	16	
4 CW-4	15	2	2	5	Alconox	0.5	2	2	2	15	15	
5 CW-5	15	2	2	5	Alconox	0.5	2	2	2	15	16	
6 CW-6	15	2	2	5	Alconox	0.5	2	2	2	15	15	

FIG. 36E

Prep Equipment Protocol - Carboy Dryer

3408

	Cycle Code	Load	Heat Up Minutes	Dry		Cool Minutes	Unload	Total
				Temp (C)	Minutes			
1	CD-1	10	30	250	40	30	10	100
2	CD-2	10	30	250	25	30	10	85
3	CD-3	10	30	250	25	30	10	85
4	CD-4	10	30	250	25	30	10	85
5	CD-5	10	30	250	25	30	10	85

FIG. 36F

3612v Prep Equipment Protocol - Steam Sterilizer

Cycles														
SS-1					SS-2					SS-3				
Press. (Bar)	Minutes To Ach.	Minutes To Hold	No. of Cycles	Subt.	Press. (Bar)	Minutes To Ach.	Minutes To Hold	No. of Cycles	Subt.	Press. (Bar)	Minutes To Ach.	Minutes To Hold	No. of Cycles	Subt.
1 Load				20					20					20
2														
3 Pre Sterilization														
4 Deep Vacuum	16	1	1	16										
5 Vacuum/Steam Pulse														
6 Vacuum														
7 Steam				18										
8 Subtotal														
9														
10 Sterilization														
11 Steam	1	20	1	60	1	20	40	1	60	1	20	40	1	60
12 Steam/Air				60					60					60
13 Subtotal														
14														
15 Cooling														
16 Direct Air Cooling	0	40	1	40	0	40	0	1	40	0	40	0	1	40
17 Indirect Jacket Cooling														
18 Overpressure				40					40					40
19 Subtotal														
20														
21 Drying	0	20	5	25										
22 Fast Exhaust														
23 Slow Exhaust														
24 Deep Vacuum														
25 Vacuum Pulse									30					30
26 Heat														
27 Heated Pressure				25					30					30
28 Subtotal														
29				20					20					20
30 Unload														
31				161					161					161
32 Total Minutes				27					27					27
33 Total Hours														

Prep Equipment Protocol - Dry Heat Sterilizer

340°

	Cycle Code	Load	Heat Up Minutes	Sterilization		Cool Minutes	Unload	Total
				Temp (C)	Minutes			
1	SO-1	15	30	250	40	20	15	130
2	SO-2	15	30	250	25	30	15	115
3	SO-3	15	30	250	25	30	15	115
4	SO-4	15	30	250	25	30	15	115
5	SO-5	15	30	250	25	30	15	115

FIG. 36 H

-Prep-Equipment Protocol - Equipment Prep Procedures

3702

3704

		EPC1	EPC2	EPC3	EPC4	EPC5	EPC6	EPC7
1	Initial Rinse							
2								
3	Bench Sink - 1							
4	Procedure Protocol	BS-1	BS-1	BS-2	BS-1			
5	Duration	PHrs. 0.33	0.33	0.33	0.33			
6	Hold/Dry	PHrs. 0	0	0				
7	Subtotal	PHrs. 0.33	0.33	0.33	0.33	0.00	0.00	0.00
8	Cumulative	PHrs. 0.33	0.33	0.33	0.33	0.00	0.00	0.00
9								
10	Wash Station - 1							
11	Procedure Protocol					WS-1	WS-1	
12	Duration	PHrs.				0.25	0.25	
13	Hold/Dry	PHrs.						
14	Subtotal	PHrs. 0.00	0.00	0.00	0.00	0.25	0.25	0.00
15	Cumulative	PHrs. 0.33333	0.33333	0.33333	0.33333	0	0	0
16								
17	Cleaning							
18								
19	Bench Sink - 1							
20	Procedure Protocol	BS-3	BS-3	BS-4				
21	Duration	PHrs. 0.33	0.33	0.33				
22	Hold/Dry	PHrs.						
23	Subtotal	PHrs. 0.33	0.33	0.33	0.00	0.00	0.00	0.00
24	Cumulative	PHrs. 0.66667	0.66667	0.66667	0.33333	0	0	0
25								
26	Glassware Washer - 1							
27	Procedure Protocol				GW-1			
28	Duration	PHrs.			0.67			
29	Hold/Dry	PHrs.						
30	Subtotal	PHrs. 0.00	0.00	0.00	0.67	0.00	0.00	0.00
31	Cumulative	PHrs. 0.66667	0.66667	0.66667	1	0	0	0
32								
33	Glassware Dryer - 1							
34	Procedure Protocol	GD-1	GD-1	GD-2	GD-3			
35	Duration	PHrs. 2.00	2.00	1.75	1.75			
36	Hold/Dry	PHrs.						
37	Subtotal	PHrs. 2.00	2.00	1.75	1.75	0.00	0.00	0.00
38	Cumulative	PHrs. 2.66667	2.66667	2.41667	2.75	0	0	0
39								
40	Carboy Washer - 1							
41	Procedure Protocol					CW-1	CW-1	
42	Duration	PHrs.				0.25	0.25	
43	Hold/Dry	PHrs.						
44	Subtotal	PHrs. 0.00	0.00	0.00	0.00	0.25	0.25	0.00
45	Cumulative	PHrs. 2.66667	2.66667	2.41667	2.75	0.25	0.25	0
46								
47	Carboy Dryer - 1							
48	Procedure Protocol					CD-1	CD-1	
49	Duration	PHrs.				1.67	1.67	
50	Hold/Dry	PHrs.						
51	Subtotal	PHrs. 0.00	0.00	0.00	0.00	1.67	1.67	0.00
52	Cumulative	PHrs. 2.66667	2.66667	2.41667	2.75	1.91667	1.91667	0
53								
54	Prep							
55								
56	Staffing		2	2	2	2	2	2
57								
58	Preassembly							
59	Man Hours	MHrs.		1				
60	Procedure Hours			0.5				

FIG. 37A

Prep Equipment Protocol - Equipment Prep Procedures

			EPC1	EPC2	EPC3	EPC4	EPC5	EPC6	EPC7
61	Cummulative	PHrs.	2.68887	3.16687	2.41687	2.75	1.91657	1.91657	0
62	Wrap								
63	Man Hours	MHrs.	1.5	1.5	1.5	1.5	1.5	1.5	1.5
64	Procedure Hours		0.75	0.75	0.75	0.75	0.75	0.75	0.75
65	Cummulative	PHrs.	3.41667	3.91667	3.16667	3.6	2.66667	2.66667	0.75
66									
67	Sterilization								
68									
69	Autoclave - 1		SS-1	SS-1	SS-1	SS-1	SS-2		SS-3
70	Procedure	PHrs.	2.68	2.68	2.68	2.68	3.25		3.83
71	Duration								
72	Hold/Dry	PHrs.							
73	Subtotal	PHrs.	2.68	2.68	2.68	2.68	3.25	0.00	3.83
74	Cummulative	PHrs.	6.10	6.80	5.85	6.18	5.92	2.67	4.58
75									
76									
77	Dry Heat - 1							SO-1	
78	Procedure							2.17	
79	Hours/Load	PHrs.							
80	Hold/Dry	PHrs.	0.00	0.00	0.00	0.00	0.00	2.17	0.00
81	Subtotal	PHrs.	6.10	6.60	5.85	6.18	5.92	4.83	4.58
82	Cummulative	PHrs.							
83									
84	Total		6.10	6.80	5.85	6.18	6.17	5.08	4.58
85									
86	Max		2.68	2.68	2.68	2.68	3.25	2.17	3.83

FIG. 37B

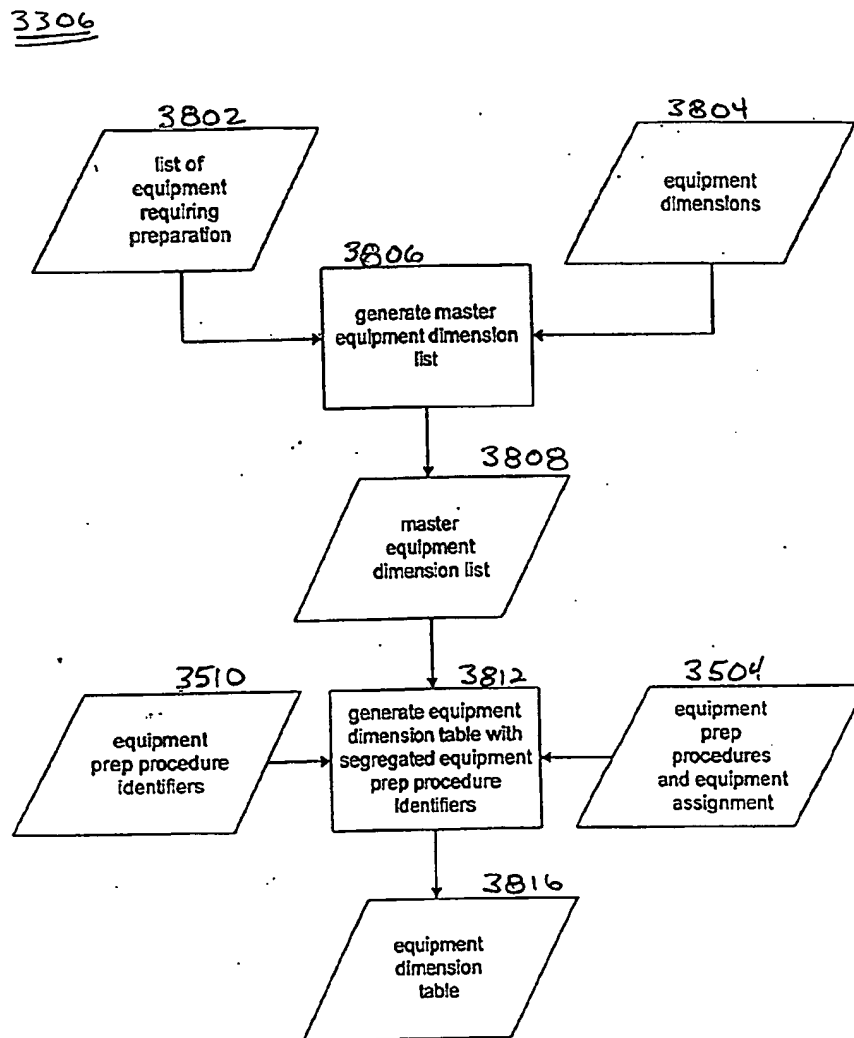
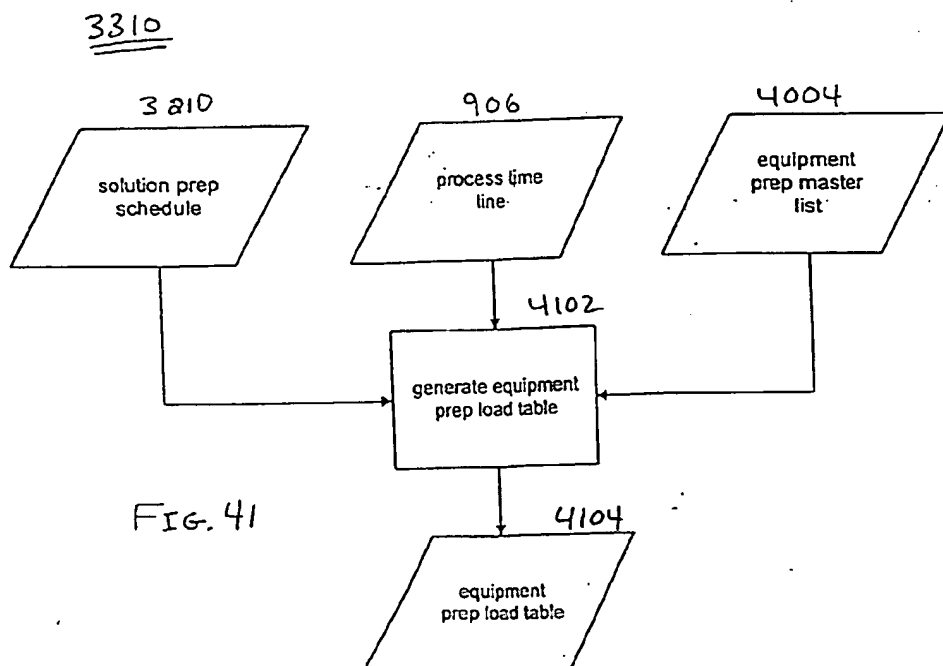
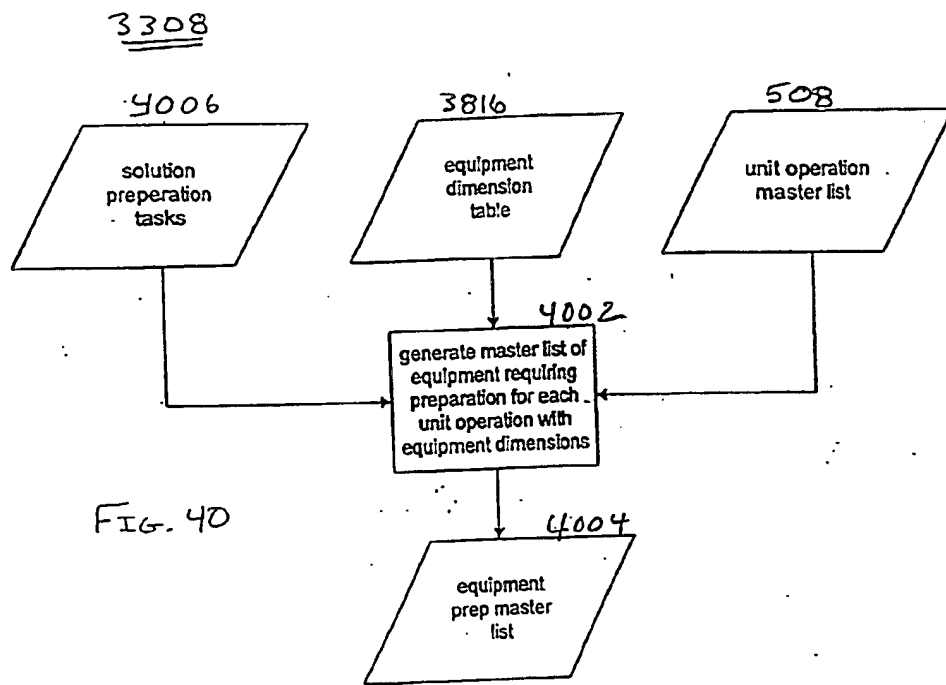


FIG. 38

Load Configuration Table - General

	EPC-1	EPC-3				EPC-4				EPC-6			
		Substructure	DO Press	PT Press	Felters	Columns	Network's	Home Bldgs	Urges	Measurements	Network Structure	Flashes Tapping	Load Capacity
	Specific Gravity	PH			Feet	Elbow				Feet	Feet	Feet	Feet
1. 1000 PSI	4	4	1	4	4	4	0	3	0	1	1	1	1
2. 750 PSI	3	2	2	2	2	2	2	2	2	2	2	2	2
3. 500 PSI	12	6	12	11	4	6	2	2	15	2	4	16	20
4. 250 PSI	08	04	50	24	04	24	24	11	14	43	41	234	194
5. 100 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
6. 50 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
7. 25 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
8. 10 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
9. 5 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
10. 2.5 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
11. 1.25 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
12. 0.625 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
13. 0.3125 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
14. 0.15625 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
15. 0.078125 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
16. 0.0390625 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
17. 0.01953125 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
18. 0.009765625 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
19. 0.0048828125 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
20. 0.00244140625 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
21. 0.001220703125 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
22. 0.0006103515625 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
23. 0.00030517578125 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
24. 0.000152587890625 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
25. 0.0000762939453125 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
26. 0.00003814697265625 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
27. 0.000019073486328125 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
28. 0.0000095367431640625 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
29. 0.00000476837158203125 PSI	02	02	02	01	03	02	01	01	01	01	01	01	01
30. 0.0000													

3904 3906 3908 3910 3912 3914 3916 3918 3920 3922



Equipment Prep Load Table

4208

4206

4204

4202

TASK -Equipment-	EPC-1		EPC-2				EPC-3					
	Unit Oper End Time Date	Specialty Glass Siphon Tubes	Total	Instruments			Fittings			Hose Barbs	Clamps	Total CF
				PI	DO Probe	pH Probe	Teas	Elbows	Crosses			
				0.03	0.08	0.08	0.03	0.02	0.08	0.01	0.01	
1 Inoculum Prep	08/04/88 02:30 PM		0									0.00
2 Flask Growth	08/05/88 01:30 PM		0									0.00
3 Seed Fermentation	08/06/88 03:30 PM		0									0.00
4 Fermentation	08/07/88 12:00 PM		0	4			6			2	18	0.50
5 Heat Exchange	08/07/88 01:00 PM		0	0.111			0.17			0.03	0.17	0.50
6 Cont. Cent/Solids	08/07/88 11:51 AM		0	3			0.11			0.03	0.08	0.22
1 Inoculum Prep	08/07/88 02:30 PM		0	0.083			0.11			0.03	0.08	0.31
2 Flask Growth	08/07/88 01:30 PM		0									0.00
3 Seed Fermentation	08/08/88 03:30 PM		0									0.00
4 Fermentation	08/08/88 09:00 AM		0	4			6			2	18	0.50
5 Heat Exchange	08/08/88 10:00 AM		0	0.111			0.17			0.03	0.17	0.50
6 Cont. Cent/Solids	08/08/88 08:51 AM		0	0.083			0.11			0.03	0.08	0.31
1 Inoculum Prep	08/08/88 02:30 PM		0	0.083			0.11			0.03	0.08	0.31
2 Flask Growth	08/08/88 01:30 PM		0									0.00
3 Seed Fermentation	08/10/88 03:30 PM		0									0.00
4 Fermentation	08/03/88 10:00 AM		0	4			6			2	18	0.50
5 Heat Exchange	08/11/88 08:00 AM		0	0.111			0.17			0.03	0.17	0.50
6 Cont. Cent/Solids	08/11/88 08:51 AM		0	0.083			0.11			0.03	0.08	0.31
7 Cell Resuspension	08/11/88 12:15 PM		0	0.083			0.11			0.03	0.08	0.31
8 Heat Exchange	08/11/88 09:33 AM		0									0.00
9 Cell Disruption	08/11/88 09:51 AM		0									0.00
10 Heat Exchange	08/11/88 10:09 AM		0									0.00

EPC 420

Equipment Items	Unitl Oper End Time DateTime		EPC-4					EPC-5					EPC-8																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
			Rubber Stoppers		Flexible Tubing Silicone 0.33	Neoprene 3.33	Total CF	Small Glassware		Total CF	PP Carboys			Total CF	BSG Carboys			Total CF																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																									
			Flasks 0.25	Silicone 0.00				Butyl 0.03	Flasks 0.03125		Beakers 0.03125	10L 1.3333	20L 4.88		45L 10.7	10L 1.3333	20L 4.88		45L 10.7																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								

FIG. 42B

Equipment Prep Load Table

4218

4220

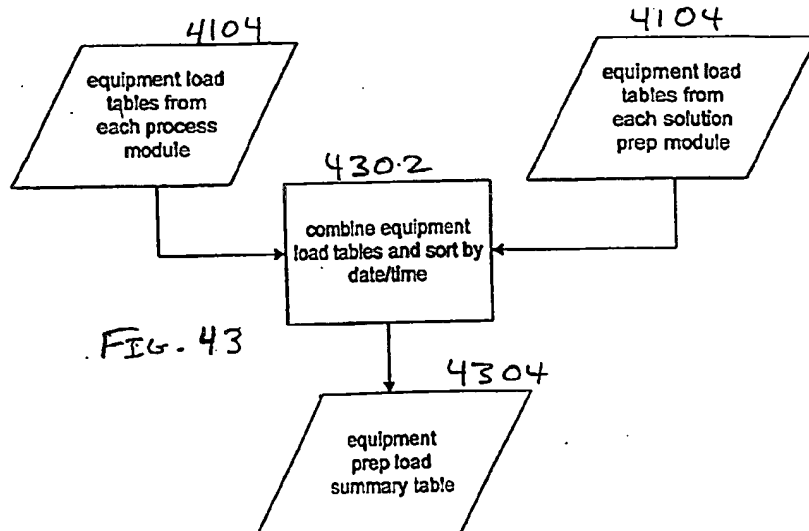
Equipment Items	Unit Oper End Time		EPC-1		EPC-2						EPC-3					
			Date	Time	Specialty Glass Syringe Tubes	Total	PI 0.03	DO Probe 0.08	pH Probe 0.08	Fittings Tees 0.03	Elbows 0.02	Crosses 0.08	Reducers 0.01	Hose Barb 0.01	Clamps 0.01	Total CF
8 Heat Exchange	08/1/88	10:27 AM				0										0.00
9 Cell Disruption	08/1/88	10:45 AM				0										0.00
10 Heat Exchange	08/1/88	12:00 AM				0										0.00
0 Heat Exchange	08/1/88	02:21 PM				0										0.00
9 Cell Disruption	08/1/88	02:39 PM				0										0.00
10 Heat Exchange	08/1/88	02:57 PM				0										0.00
11 IB Resuspension	08/1/88	10:57 AM				0										0.00
12 Centrifugation	08/1/88	11:33 AM				0										0.00
11 IB Resuspension	08/1/88	03:08 PM				0										0.00
12 Centrifugation	08/1/88	03:12 PM				0										0.00
13 Renaturation	08/12/88	08:43 AM				0										0.00
14 Buffer Exchange	08/12/88	11:47 AM				0										0.00
16 Clarification	08/12/88	11:03 AM				0										0.00
10 Chromatography 1	08/12/88	03:59 PM				0										0.00
17 Chromatography 2	08/12/88	08:59 PM				0										0.00
18 Buffer Exchange	08/12/88	08:27 PM				0										0.00
19 Chromatography 3	08/12/88	10:07 PM				0										0.00
20 Buffer Exchange	08/12/88	10:38 PM				0										0.00
21 Chromatography 4	08/13/88	12:14 AM				0										0.00
22 Sterile Filtration	08/13/88	12:48 AM				0										0.00
Totals																3.26

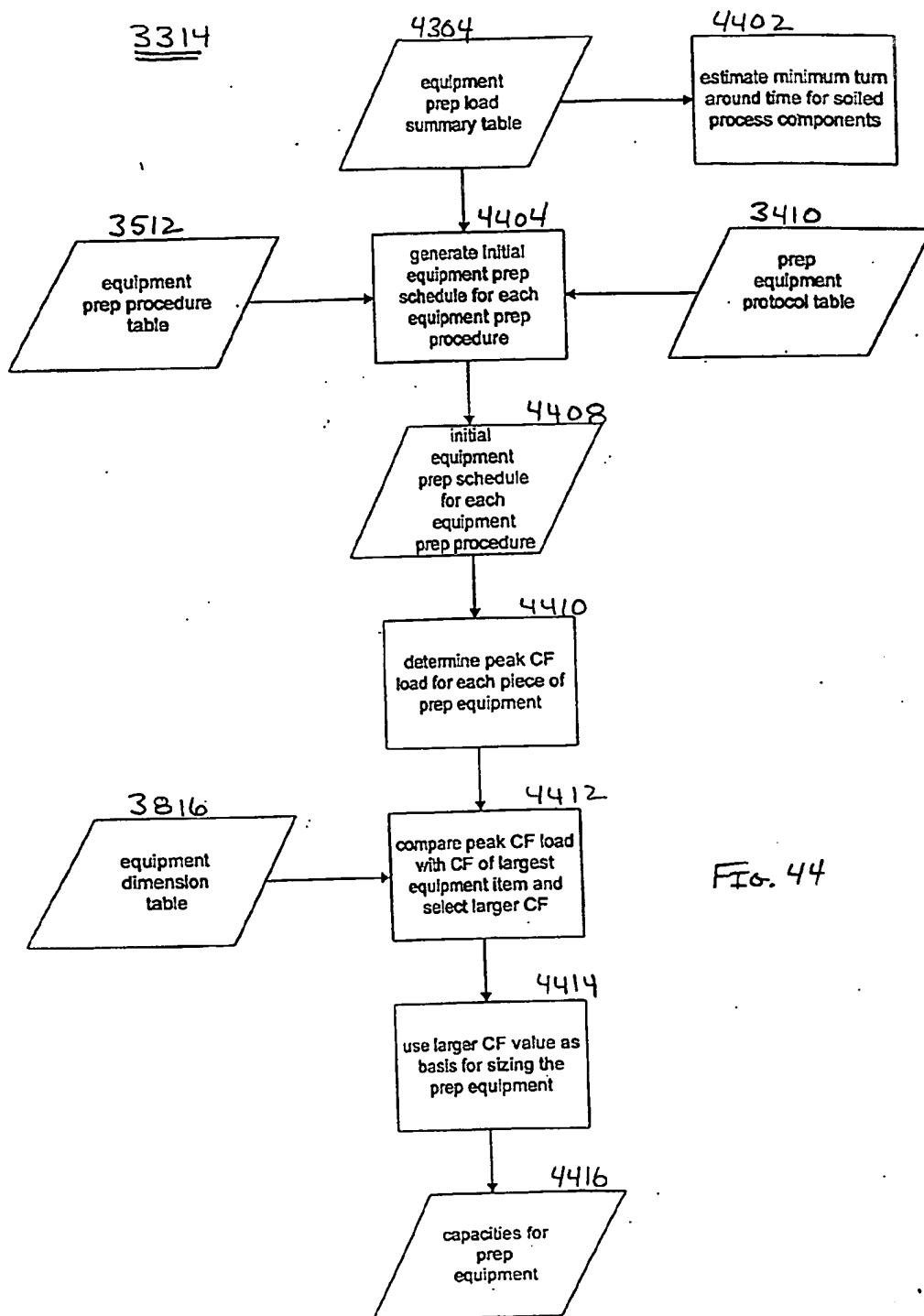
FIG 42C

Equipment: Top Load Table

Equipment Items	Unit Oper End Time		EPC-4				EPC-5				EPC-8			
			Rubber Stoppers		Flexible Tubing		Small Glassware		Total CF		PP Carboys		Total CF	
	Date	Time	Sicoro 0.00	Butyl 0.00	Silicone 0.33	Neoprene 3.33	Beakers 0.03125	Flasks 0.25			10L 1.3333	20L 4.88	45L 10.7	
8 Heat Exchange	08/11/98	10:27 AM							0.00					0.00
9 Cell Disruption	08/11/98	10:45 AM							0.00					0.00
10 Heat Exchange	08/11/98	12:00 AM							0.00					0.00
8 Heat Exchange	08/11/98	02:21 PM							0.00					0.00
9 Cell Disruption	08/11/98	02:39 PM							0.00					0.00
10 Heat Exchange	08/11/98	02:57 PM							0.00					0.00
11 IS Resuspension	08/11/98	10:57 AM							0.00					0.00
12 Centrifugation	08/11/98	11:33 AM							0.00					0.00
11 IB Resuspension	08/11/98	03:09 PM							0.00					0.00
12 Centrifugation	08/11/98	03:12 PM							0.00					0.00
13 Renaturation	08/12/98	05:43 AM							0.00					0.00
14 Buffer Exchange	08/12/98	11:47 AM							0.00					0.00
16 Clarification	08/12/98	11:03 AM							0.00					0.00
16 Chromatography 1	08/12/98	03:59 PM							0.00					0.00
17 Chromatography 2	08/12/98	06:58 PM							0.00					0.00
18 Buffer Exchange	08/12/98	05:27 PM							0.00					0.00
19 Chromatography 3	08/12/98	10:07 PM							0.00					0.00
20 Buffer Exchange	08/12/98	10:38 PM							0.00					0.00
21 Chromatography 4	08/13/98	12:14 AM							0.00					0.00
22 Sterile Filtration	08/13/98	12:48 AM							0.00					0.00
Totals														

FIG. 42D

3312



4506

QC Load Table - PE Module

4504

4502

Operation	QA/QC Samples										Immunochemical									
	Start		Finish		Time		Date		Time		Date		Time		Date		Time		Date	
	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time
1 A Inoculum Prep	06/03/96	08:00 AM																		
2 Set Up	06/03/96	08:30 AM	06/03/96	12:30 PM																
3 Pre-Inoculation	06/03/96	12:30 PM	06/03/96	03:30 PM																
4 Inoculation	06/03/96	03:30 PM	06/04/96	02:30 PM																
5 Clean Up	06/04/96	02:30 PM	06/04/96	02:45 PM																
6 Subtotal																				
7																				
8 2 A Flask Growth																				
9 Set Up	06/04/96	12:30 PM	06/04/96	01:30 PM																
10 Pre-Inoculation	06/04/96	01:30 PM	06/04/96	02:30 PM																
11 Inoculation	06/04/96	02:30 PM	06/05/96	01:30 PM																
12 Clean Up	06/05/96	01:30 PM	06/05/96	01:45 PM																
13 Subtotal																				
14																				
15 3 A Grad Fermentation																				
16 Set Up	06/05/96	11:30 AM	06/05/96	12:30 PM																
17 Pre-Inoculation	06/05/96	12:30 PM	06/05/96	01:30 PM																
18 Fermentation	06/05/96	01:30 PM	06/06/96	10:30 AM																
19 Harvest	06/06/96	10:30 AM	06/06/96	11:30 AM																
20 CIP	06/06/96	11:30 AM	06/06/96	12:30 PM																
21 SIP	06/06/96	12:30 PM	06/06/96	03:30 PM																
22 Clean Up	06/06/96	03:30 PM	06/06/96	03:30 PM																
23 Subtotal																				
24																				
25																				
26 4 A Production Fermentation																				
27 Set Up	06/06/96	08:00 AM	06/06/96	10:00 AM																
28 Pre-Inoculation	06/06/96	10:00 AM	06/06/96	11:00 AM																
29 Fermentation	06/06/96	11:00 AM	06/07/96	08:00 AM																
30 CIP	06/07/96	08:00 AM	06/07/96	09:00 AM																
31 SIP	06/07/96	09:00 AM	06/07/96	10:00 AM																
32 Clean Up	06/07/96	10:00 AM	06/07/96	12:00 PM																
33 Subtotal																				
34																				
35																				
36 5 A Heat Exchange																				
37 Set Up	06/07/96	08:00 AM	06/07/96	08:30 AM																
38 Transfer	06/07/96	08:30 AM	06/07/96	09:00 AM																
39 CIP	06/07/96	09:00 AM	06/07/96	10:00 AM																
40 SIP	06/07/96	10:00 AM	06/07/96	11:00 AM																
41 Clean Up	06/07/96	11:00 AM	06/07/96	01:00 PM																
42 Subtotal																				
43																				
44																				
45 6 A Cont. Cent. Solids																				
46 Set Up	06/07/96	08:30 AM	06/07/96	09:00 AM																
47																				

Fig. 45A

4506

QC Load Table - PE Module

Operation		QA/QC Samples										Biochemical										Immunology		Acl
		Start		Finish		Chemical					Visual					Biochemical					Immunology			
		Date	Time	Date	Time	AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AC-6	AB-1	AB-2	AB-3	AB-4	AB-5	AB-6	AB-7	AI-1	AI-2	AA-1	
48	Centrifugation	08/03/98	08:00 AM	08/07/98	10:00 AM																			
49	Wash	08/07/98	10:00 AM	08/07/98	10:30 AM																			
50	CIP	08/07/98	10:00 AM	08/07/98	10:21 AM																			
51	SIP	08/07/98	10:21 AM	08/07/98	11:21 AM																			
52	Clean Up	08/07/98	11:21 AM	08/07/98	11:51 AM																			
53	Sub Total																							
54	1 B Incubation Prep																							
55	Set Up	08/03/98	01:30 PM	08/03/98	02:30 PM																			
56	Preincubation	08/03/98	02:30 PM	08/03/98	03:30 PM																			
57	Incubation	08/03/98	03:30 PM	08/04/98	02:45 PM																			
58	Clean Up	08/04/98	02:30 PM	08/04/98	02:45 PM																			
59	Subtotal																							
60																								
61	2 B First Growth																							
62	Set Up	08/04/98	12:30 PM	08/04/98	01:30 PM																			
63	Preincubation	08/04/98	01:30 PM	08/04/98	02:30 PM																			
64	Incubation	08/04/98	02:30 PM	08/05/98	01:45 PM																			
65	Clean Up	08/05/98	01:30 PM	08/05/98	01:45 PM																			
66	Subtotal																							
67																								
68	3 B Seed Fermentation																							
69	Set Up	08/05/98	11:30 AM	08/05/98	12:30 PM																			
70	Preincubation	08/05/98	12:30 PM	08/05/98	01:30 PM																			
71	Fermentation	08/05/98	01:30 PM	08/05/98	10:30 AM																			
72	Harvest	08/05/98	10:30 AM	08/05/98	11:00 AM																			
73	CIP	08/05/98	10:30 AM	08/05/98	11:30 AM																			
74	SIP	08/05/98	11:30 AM	08/05/98	12:30 PM																			
75	Clean Up	08/05/98	12:30 PM	08/05/98	03:30 PM																			
76	Subtotal																							
77																								
78																								
79	4 B Production Fermentation																							
80	Set Up	08/06/98	09:00 AM	08/06/98	10:00 AM																			
81	Preincubation	08/06/98	10:00 AM	08/06/98	11:00 AM																			
82	Fermentation	08/06/98	11:00 AM	08/07/98	05:00 AM																			
83	CIP	08/07/98	03:00 AM	08/07/98	05:00 AM																			
84	SIP	08/07/98	05:00 AM	08/07/98	10:00 AM																			
85	Clean Up	08/07/98	10:00 AM	08/07/98	12:30 PM																			
86	Subtotal																							
87																								
88																								
89	6 B Heat Exchange																							
90	Set Up	08/07/98	05:00 AM	08/07/98	05:30 AM																			
91	Transfer	08/07/98	05:00 AM	08/07/98	10:00 AM																			
92	CIP	08/07/98	05:00 AM	08/07/98	10:00 AM																			
93																								
94																								

Fig. 45B

QC Log Table - PE Module

Operation	QA/QC Samples																																		
	Start				Finish				Visual								Chemical								Biological								Immunological		Act.
	Date	Time	Date	Time	AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AC-6	AB-1	AB-2	AB-3	AB-4	AB-5	AB-6	AB-7	AB-8	AB-9	AB-10	AB-11	AB-12											
SIP	06/07/98	06:00 AM	06/07/98	11:00 AM																															
Clean Up	06/07/98	10:00 AM	06/07/98	01:00 PM																															
Subtotal	06/07/98	11:00 AM	06/07/98																																
6 B Cont. Gant./Solids																																			
Get Up	06/07/98	06:00 AM	06/07/98	06:00 AM																															
Certification	06/07/98	06:00 AM	06/07/98	10:00 AM																															
Wash	06/07/98	10:00 AM	06/07/98	10:21 AM																															
CIP	06/07/98	10:00 AM	06/07/98	10:21 AM																															
SIP	06/07/98	10:21 AM	06/07/98	11:21 AM																															
Clean Up	06/07/98	11:21 AM	06/07/98	11:31 AM																															
Sub Total	06/07/98																																		
1 C Inoculum Prep																																			
Set Up	06/03/98	01:30 PM	06/03/98	02:30 PM																															
Preincubation	06/03/98	02:30 PM	06/03/98	03:30 PM																															
Incubation	06/03/98	03:30 PM	06/03/98	02:30 PM																															
Clean Up	06/03/98	02:30 PM	06/03/98	02:45 PM																															
Subtotal	06/03/98																																		
2 C Flask Growth																																			
Set Up	06/04/98	12:30 PM	06/04/98	01:30 PM																															
Preincubation	06/04/98	01:30 PM	06/04/98	02:30 PM																															
Incubation	06/04/98	02:30 PM	06/04/98	01:30 PM																															
Clean Up	06/04/98	01:30 PM	06/04/98	01:45 PM																															
Subtotal	06/04/98																																		
3 C Used Fermentation																																			
Set Up	06/05/98	11:30 AM	06/05/98	12:30 PM																															
Preincubation	06/05/98	12:30 PM	06/05/98	01:30 PM																															
Fermentation	06/05/98	01:30 PM	06/05/98	06:00 PM																															
Harvest	06/05/98	10:30 AM	06/05/98	11:00 AM																															
CIP	06/05/98	10:30 AM	06/05/98	11:30 AM																															
SIP	06/05/98	11:30 AM	06/05/98	12:30 PM																															
Clean Up	06/05/98	12:30 PM	06/05/98	03:30 PM																															
Subtotal	06/05/98																																		
4 C Production Fermentation																																			
Set Up	06/06/98	09:00 AM	06/06/98	10:00 AM																															
Preincubation	06/06/98	10:00 AM	06/06/98	11:00 AM																															
Fermentation	06/06/98	11:00 AM	06/07/98	06:00 AM																															
CIP	06/07/98	06:00 AM	06/07/98	06:00 AM																															
SIP	06/07/98	06:00 AM	06/07/98	10:00 AM																															
Clean Up	06/07/98	10:00 AM	06/07/98	12:00 PM																															
Subtotal	06/07/98																																		
5 C Production Fermentation																																			
Set Up	06/06/98	09:00 AM	06/06/98	10:00 AM																															
Preincubation	06/06/98	10:00 AM	06/07/98	06:00 AM																															
Fermentation	06/06/98	11:00 AM	06/07/98	06:00 AM																															
CIP	06/07/98	06:00 AM	06/07/98	06:00 AM																															
SIP	06/07/98	06:00 AM	06/07/98	10:00 AM																															
Clean Up	06/07/98	10:00 AM	06/07/98	12:00 PM																															
Subtotal	06/07/98																																		
6 C Production Fermentation																																			
Set Up	06/06/98	09:00 AM	06/06/98	10:00 AM																															
Preincubation	06/06/98	10:00 AM	06/07/98	06:00 AM																															
Fermentation	06/06/98	11:00 AM	06/07/98	06:00 AM																															
CIP	06/07/98	06:00 AM	06/07/98	06:00 AM																															
SIP	06/07/98	06:00 AM	06/07/98	10:00 AM																															
Clean Up	06/07/98	10:00 AM	06/07/98	12:00 PM																															
Subtotal	06/07/98																																		
7 C Production Fermentation																																			
Set Up	06/06/98	09:00 AM	06/06/98	10:00 AM																															
Preincubation	06/06/98	10:00 AM	06/07/98	06:00 AM																															
Fermentation	06/06/98	11:00 AM	06/07/98	06:00 AM																															
CIP	06/07/98	06:00 AM	06/07/98	06:00 AM																															
SIP	06/07/98	06:00 AM	06/07/98	10:00 AM																															
Clean Up	06/07/98	10:00 AM	06/07/98	12:00 PM																															
Subtotal	06/07/98																																		
8 C Production Fermentation																																			
Set Up	06/06/98	09:00 AM	06/06/98	10:00 AM																															
Preincubation	06/06/98	10:00 AM	06/07/98	06:00 AM																															
Fermentation	06/06/98	11:00 AM	06/07/98	06:00 AM																															
CIP	06/07/98	06:00 AM	06/07/98	06:00 AM																															
SIP	06/07/98	06:00 AM	06/07/98	10:00 AM																															
Clean Up	06/07/98	10:00 AM	06/07/98	12:00 PM																															
Subtotal	06/07/98																																		
9 C Production Fermentation																																			
Set Up	06/06/98	09:00 AM	06/06/98	10:00 AM																															
Preincubation	06/06/98	10:00 AM	06/07/98	06:00 AM																															
Fermentation	06/06/98	11:00 AM	06/07/98	06:00 AM																															
CIP	06/07/98	06:00 AM	06/07/98	06:00 AM																															
SIP	06/07/98	06:00 AM	06/07/98	10:00 AM																															
Clean Up	06/07/98	10:00 AM	06/07/98	12:00 PM																															
Subtotal	06/07/98																																		
10 C Production Fermentation																																			
Set Up	06/06/98	09:00 AM	06/06/98	10:00 AM																															
Preincubation	06/06/98	10:00 AM	06/07/98	06:00 AM																															
Fermentation	06/06/98	11:00 AM	06/07/98	06:00 AM																															
CIP	06/07/98	06:00 AM	06/07/98	06:00 AM																															
SIP	06/07/98	06:00 AM	06/07/98	10:00 AM																															
Clean Up	06/07/98	10:00 AM	06/07/98	12:00 PM																															
Subtotal	06/07/98																																		
11 C Production Fermentation																		</																	

FIG. 45C

QC Load Table - PE Module

Operation	QA/QC Samples										Biochemical										Immuno(ge)l		Act.
	Start		Finish		Chemical					Biochemical					Immuno(ge)l								
	Date	Time	Date	Time	AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AC-6	AB-1	AB-2	AB-3	AB-4	AB-5	AB-6	AB-7	AI-1	AI-2	AA-1	
Subtotal	03/03/00	03:00 AM																					
5 C Heat Exchange																							
Set Up	06/07/98	08:00 AM	06/07/98	08:30 AM																			
Transfer	06/07/98	08:30 AM	06/07/98	09:30 AM																			
CIP	06/07/98	09:30 AM	06/07/98	10:30 AM																			
SIP	06/07/98	10:30 AM	06/07/98	11:30 AM																			
Clean Up	06/07/98	11:30 AM	06/07/98	01:00 PM																			
Subtotal																							
6 C Cont. Cent./Solids																							
Set Up	06/07/98	08:00 AM	06/07/98	08:00 AM																			
Centrifugation	06/07/98	08:00 AM	06/07/98	10:00 AM																			
Wash	06/07/98	10:00 AM	06/07/98	10:30 AM																			
CIP	06/07/98	10:30 AM	06/07/98	10:21 AM																			
SIP	06/07/98	10:21 AM	06/07/98	11:21 AM																			
Clean Up	06/07/98	11:21 AM	06/07/98	11:31 AM																			
Sub Total																							
7 A Resolubilization																							
Set Up	06/07/98	09:05 AM	06/07/98	10:00 AM																			
Drison	06/07/98	10:00 AM	06/07/98	10:30 AM																			
Agitate	06/07/98	10:30 AM	06/07/98	11:30 AM																			
CIP	06/07/98	11:30 AM	06/07/98	12:30 PM																			
SIP	06/07/98	12:30 PM	06/07/98	01:30 PM																			
Clean Up	06/07/98	01:30 PM	06/07/98	02:30 PM																			
Subtotal																							
8 A Heat Exchange																							
Set Up	06/07/98	11:00 AM	06/07/98	11:30 AM																			
Transfer	06/07/98	11:30 AM	06/07/98	11:54 AM																			
CIP	06/07/98	11:54 AM	06/07/98	11:54 AM																			
SIP	06/07/98	11:54 AM	06/07/98	11:54 AM																			
Clean Up	06/07/98	11:54 AM	06/07/98	11:54 AM																			
Subtotal																							
9 A Homogenization																							
Set Up	06/07/98	11:30 AM	06/07/98	11:54 AM																			
Lysis	06/07/98	11:54 AM	06/07/98	12:34 PM																			
CIP	06/07/98	12:34 PM	06/07/98	12:34 PM																			
SIP	06/07/98	12:34 PM	06/07/98	12:34 PM																			
Clean Up	06/07/98	12:34 PM	06/07/98	12:34 PM																			
Sub Total																							

FIG. 45D

QC Load Table - PE Module

Operation	QA/QC Samples										Immunochemical									
	Start		Finish		Time		Date		Time		Date		Time		Date		Time		Date	
	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time	Date	Time
10 A Heat Exchange	08/03/98	08:00 AM																		
Set Up	08/07/98	12:04 PM	08/07/98	12:34 PM																
Transfer	08/07/98	12:34 PM	08/07/98	12:52 PM																
CIP	08/07/98	12:52 PM	08/07/98	12:52 PM																
SIP	08/07/98	12:52 PM	08/07/98	12:52 PM																
Clean Up	08/07/98	12:52 PM	08/07/98	12:52 PM																
Subtotal																				
10 B Heat Exchange																				
Set Up	08/07/98	12:52 PM	08/07/98	12:52 PM																
Transfer	08/07/98	12:52 PM	08/07/98	01:10 PM																
CIP	08/07/98	01:10 PM	08/07/98	01:10 PM																
SIP	08/07/98	01:10 PM	08/07/98	01:10 PM																
Clean Up	08/07/98	01:10 PM	08/07/98	01:10 PM																
Subtotal																				
9 U Homogenization																				
Set Up	08/07/98	01:10 PM	08/07/98	01:10 PM																
Lysis	08/07/98	01:10 PM	08/07/98	01:51 PM																
CIP	08/07/98	01:51 PM	08/07/98	01:51 PM																
SIP	08/07/98	01:51 PM	08/07/98	01:51 PM																
Clean Up	08/07/98	01:51 PM	08/07/98	01:51 PM																
SUB Total																				
10 B Heat Exchange																				
Set Up	08/07/98	01:21 PM	08/07/98	01:51 PM																
Transfer	08/07/98	01:51 PM	08/07/98	02:09 PM																
CIP	08/07/98	02:09 PM	08/07/98	02:09 PM																
SIP	08/07/98	02:09 PM	08/07/98	02:09 PM																
Clean Up	08/07/98	02:09 PM	08/07/98	02:09 PM																
Subtotal																				
8 C Heat Exchange																				
Set Up	08/07/98	02:09 PM	08/07/98	02:09 PM																
Transfer	08/07/98	02:09 PM	08/07/98	02:27 PM																
CIP	08/07/98	02:27 PM	08/07/98	02:27 PM																
SIP	08/07/98	02:27 PM	08/07/98	04:27 PM																
Clean Up	08/07/98	04:27 PM	08/07/98	05:27 PM																
Subtotal																				
9 C Homogenization																				
Set Up	08/07/98	02:27 PM	08/07/98	02:27 PM																
Lysis	08/07/98	02:27 PM	08/07/98	03:07 PM																

FIG. 45E

QC Load Table - PE Module

	Operation	QACG Samples										Immunochemical									
		Start		Finish		Visual		Chemical		Biochemical		AB-1		AB-2		AB-3		AB-4		AB-6	
		Date	Time	Date	Time	AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AC-6	AB-1	AB-2	AB-3	AB-4	AB-6	AB-7	AB-1	AB-2
240	CIP	08/07/98	03:00 AM	08/07/98	04:07 PM																
241	SIP	08/07/98	04:07 PM	08/07/98	05:07 PM																
242	Clean Up	08/07/98	05:07 PM	08/07/98	06:07 PM																
243	Sub Total																				
244	10 C Heat Exchange																				
245	Set Up	09/07/98	03:07 PM	09/07/98	03:07 PM																
246	Transfer	09/07/98	03:07 PM	09/07/98	03:25 PM																
247	CIP	09/07/98	03:25 PM	09/07/98	04:25 PM																
248	SIP	09/07/98	04:25 PM	09/07/98	05:25 PM																
249	Clean Up	09/07/98	05:25 PM	09/07/98	06:25 PM																
250	Sub Total																				
251	11 A Resubtilization																				
252	Set Up	09/07/98	11:52 AM	09/07/98	12:52 PM																
253	Run	09/07/98	12:52 PM	09/07/98	01:52 PM																
254	Agitate	09/07/98	01:52 PM	09/07/98	01:52 PM																
255	CIP	09/07/98	01:52 PM	09/07/98	01:52 PM																
256	SIP	09/07/98	01:52 PM	09/07/98	01:52 PM																
257	Clean Up	09/07/98	01:52 PM	09/07/98	01:52 PM																
258	Sub Total																				
259	12 A Cont. Cent/Solids																				
260	Set Up	09/07/98	12:52 PM	09/07/98	01:52 PM																
261	Run	09/07/98	01:52 PM	09/07/98	02:22 PM																
262	Wash	09/07/98	02:22 PM	09/07/98	02:28 PM																
263	CIP	09/07/98	02:28 PM	09/07/98	02:28 PM																
264	SIP	09/07/98	02:28 PM	09/07/98	02:28 PM																
265	Clean Up	09/07/98	02:28 PM	09/07/98	02:28 PM																
266	Sub Total																				
267	11 B Resubtilization																				
268	Set Up	09/07/98	02:28 PM	09/07/98	02:28 PM																
269	Run	09/07/98	02:28 PM	09/07/98	03:13 PM																
270	Agitate	09/07/98	03:13 PM	09/07/98	04:13 PM																
271	CIP	09/07/98	04:13 PM	09/07/98	05:13 PM																
272	SIP	09/07/98	05:13 PM	09/07/98	06:13 PM																
273	Clean Up	09/07/98	06:13 PM	09/07/98	06:13 PM																
274	Sub Total																				
275	12 B Cont. Cent/Solids																				
276	Set Up	09/07/98	02:13 PM	09/07/98	03:13 PM																
277	Run	09/07/98	03:13 PM	09/07/98	03:43 PM																
278	Agitate	09/07/98	03:43 PM	09/07/98	03:48 PM																
279	CIP	09/07/98	03:48 PM	09/07/98	03:48 PM																
280	SIP	09/07/98	03:48 PM	09/07/98	03:48 PM																
281	Clean Up	09/07/98	03:48 PM	09/07/98	03:48 PM																
282	Sub Total																				
283	13 A Cont. Cent/Solids																				
284	Set Up	09/07/98	02:13 PM	09/07/98	03:13 PM																
285	Run	09/07/98	03:13 PM	09/07/98	03:43 PM																
286	Agitate	09/07/98	03:43 PM	09/07/98	03:48 PM																
287	CIP	09/07/98	03:48 PM	09/07/98	03:48 PM																
288	SIP	09/07/98	03:48 PM	09/07/98	03:48 PM																
289	Clean Up	09/07/98	03:48 PM	09/07/98	03:48 PM																
290	Sub Total																				

FIG. 45F

QC Load Table - PE Module

	Operation	QA/QC Samples										Immunological										Act.
		Start		Finish		Chemical				Visual		Biochemical										
		Date	Time	Date	Time	AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AC-6	AB-1	AB-2	AB-3	AB-4	AB-5	AB-6	AB-7	AI-1	AI-2
318	Elute A	08/03/98	01:52 PM	08/03/98	03:12 PM																	
319	Elute B	08/03/98	03:12 PM	08/03/98	03:25 PM																	
320	Regenerate	08/03/98	03:25 PM	08/03/98	03:52 PM																	
342	CIP	08/03/98	03:52 PM	08/03/98	04:52 PM																	
343	SIP	08/03/98	04:52 PM	08/03/98	05:52 PM																	
344	Clean Up	08/03/98	05:52 PM	08/03/98	06:52 PM																	
345	Sub Total																					
346																						
347	17 A PIA MPLC																					
348	Equilibration	08/03/98	02:59 PM	08/03/98	03:38 PM																	
349	Load	08/03/98	03:12 PM	08/03/98	04:17 PM																	
350	Wash	08/03/98	04:17 PM	08/03/98	05:03 PM																	
351	Elute A	08/03/98	05:03 PM	08/03/98	05:49 PM																	
352	Elute B	08/03/98	05:49 PM	08/03/98	06:57 PM																	
353	Regenerate	08/03/98	06:57 PM	08/03/98	08:13 PM																	
354	Stroke	08/03/98	08:13 PM	08/03/98	07:13 PM																	
355	CIP	08/03/98	07:13 PM	08/03/98	08:13 PM																	
356	SIP	08/03/98	08:13 PM	08/03/98	09:13 PM																	
357	Clean Up	08/03/98	09:13 PM	08/03/98	09:13 PM																	
358	Sub Total																					
359																						
360	18 A Flow Galyals																					
361	Set Up	08/03/98	03:29 PM	08/03/98	04:29 PM																	
362	Flush	08/03/98	04:29 PM	08/03/98	05:09 PM																	
363	Purge	08/03/98	05:09 PM	08/03/98	05:49 PM																	
364	Dialysis	08/03/98	05:49 PM	08/03/98	06:49 PM																	
365	Wash	08/03/98	06:49 PM	08/03/98	07:09 PM																	
366	Flush	08/03/98	07:09 PM	08/03/98	07:49 PM																	
367	Stroke	08/03/98	07:49 PM	08/03/98	08:49 PM																	
368	CIP	08/03/98	08:49 PM	08/03/98	09:49 PM																	
369	SIP	08/03/98	09:49 PM	08/03/98	10:49 PM																	
370	Clean Up	08/03/98	10:49 PM	08/03/98	10:49 PM																	
371	Sub Total																					
372																						
373	19 A PIA MPLC																					
374	Equilibration	08/03/98	03:59 PM	08/03/98	06:31 PM																	
375	Load	08/03/98	06:31 PM	08/03/98	07:03 PM																	
376	Wash	08/03/98	07:03 PM	08/03/98	08:20 PM																	
377	Elute A	08/03/98	08:20 PM	08/03/98	09:20 PM																	
378	Elute B	08/03/98	09:20 PM	08/03/98	09:39 PM																	
379	Regenerate	08/03/98	09:39 PM	08/03/98	10:39 PM																	
380	Stroke	08/03/98	10:39 PM	08/03/98	10:39 PM																	
381	CIP	08/03/98	10:39 PM	08/03/98	10:39 PM																	
382	SIP	08/03/98	10:39 PM	08/03/98	10:39 PM																	
383	Clean Up	08/03/98	10:39 PM	08/03/98	10:39 PM																	
384	Sub Total																					
385																						

FIG- 45H

QC Load Table - PE Module

	Operation	QA/QC Samples										Biochemical										Immunological		Act																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																	
		Start		Finish		Visual		Chemical		AC-1		AC-2		AC-3		AC-4		AC-5		AB-1		AB-2			AB-3		AB-4		AB-5		AB-6		AB-7		AI-1		AI-2																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				
		Date	Time	Date	Time	AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AC-6	AB-1	AB-2	AB-3	AB-4	AB-5	AB-6	AB-7	AI-1	AI-2																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																			
307	Clean Up	06/03/96	06:00 AM																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						

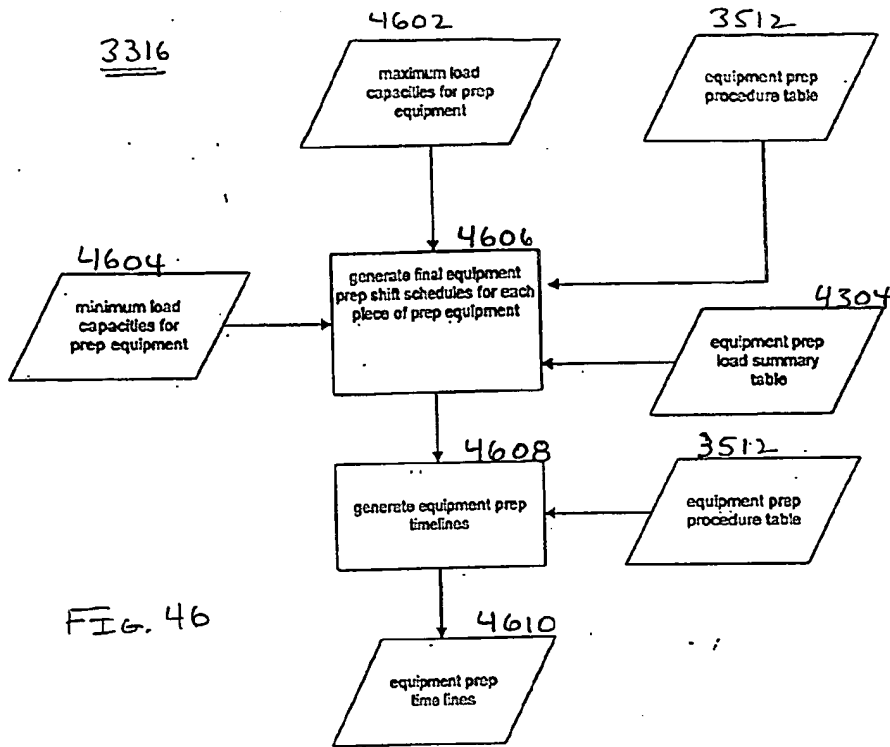


FIG. 46

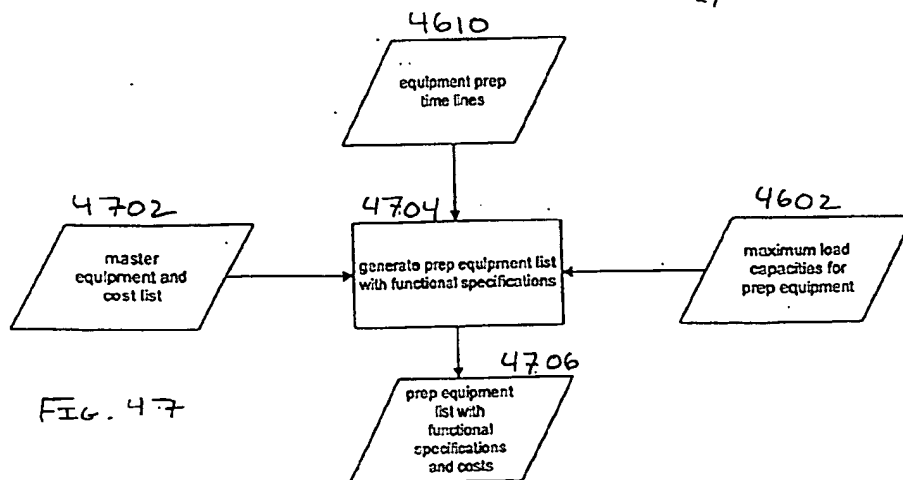


FIG. 47

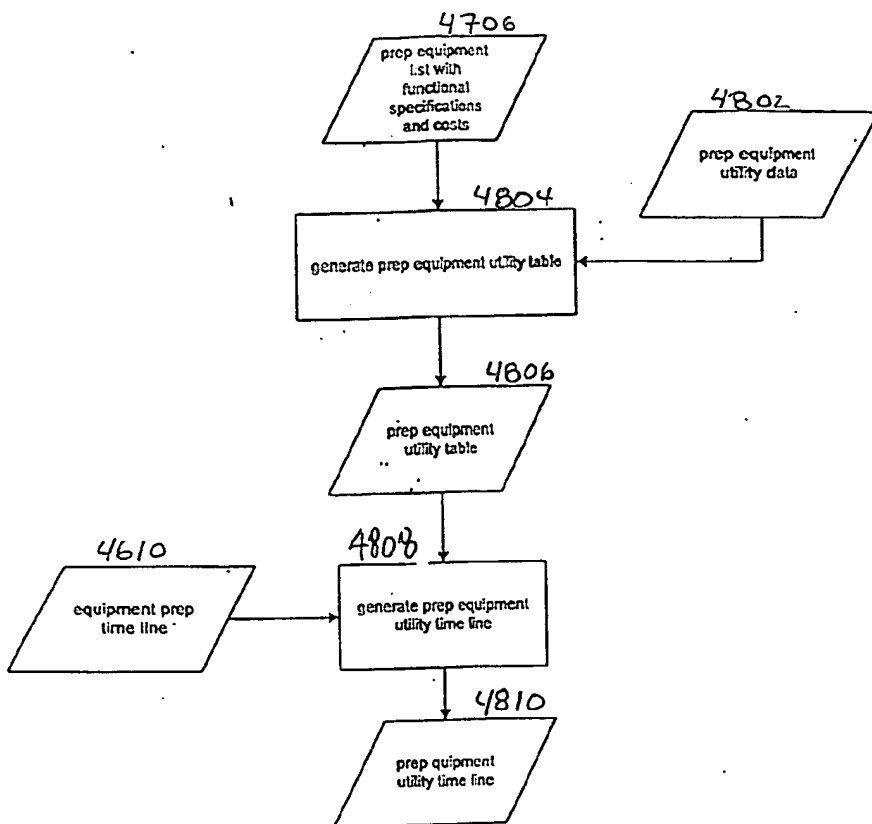
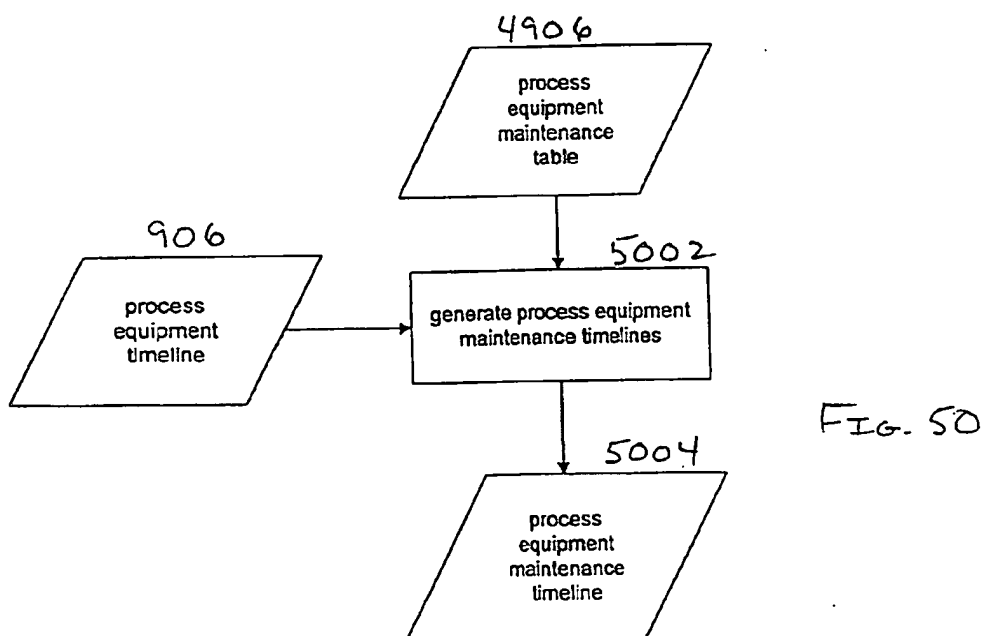
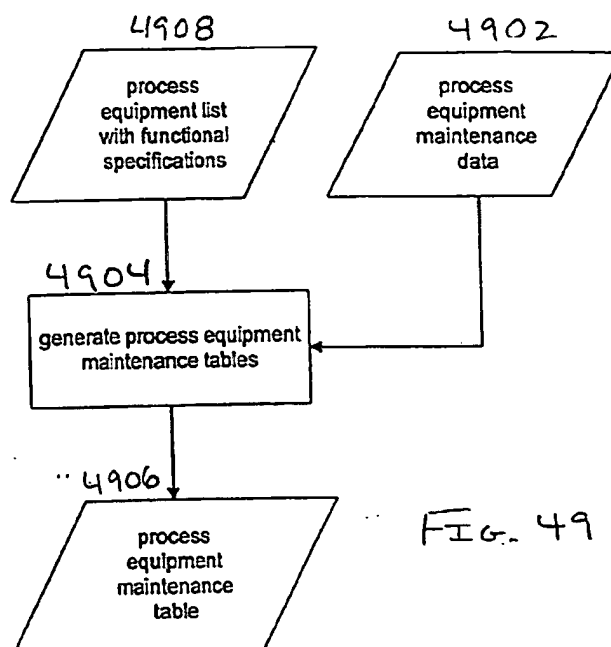
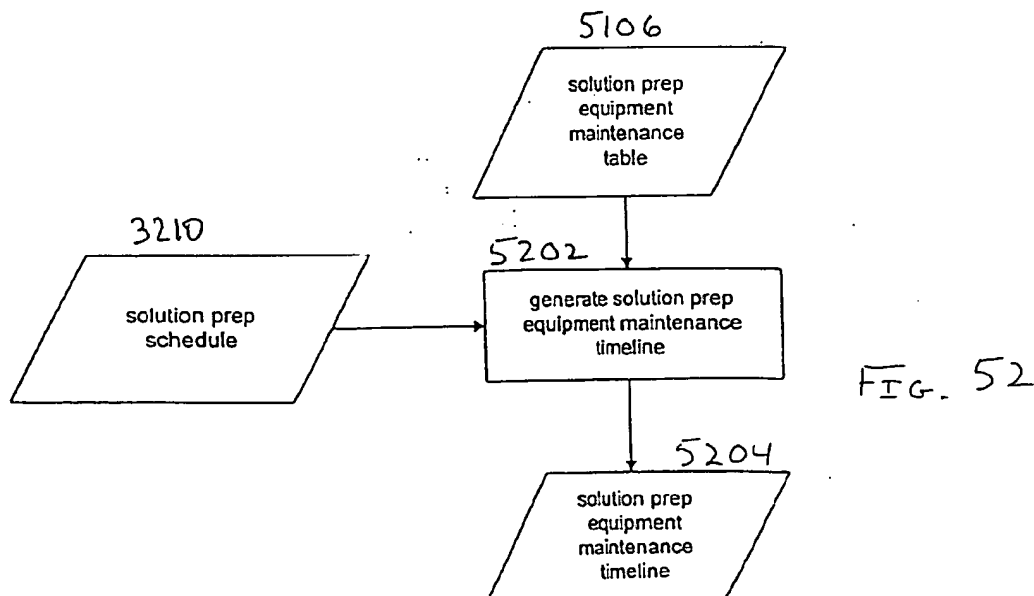
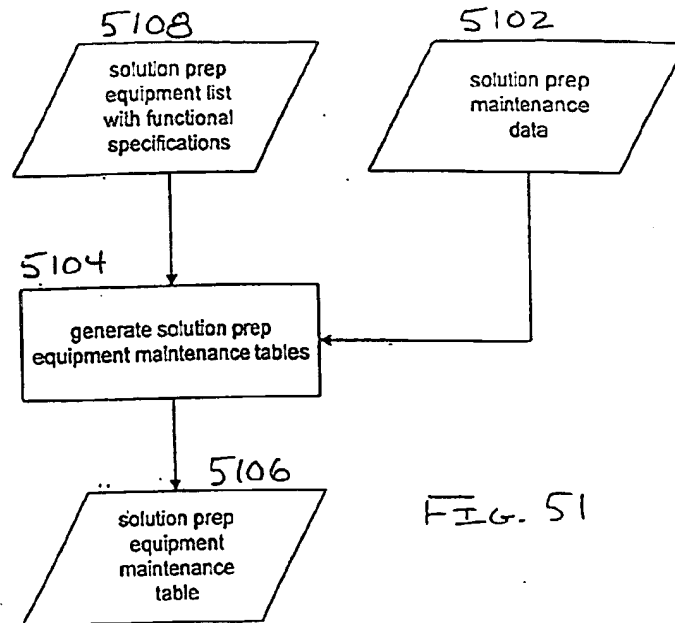
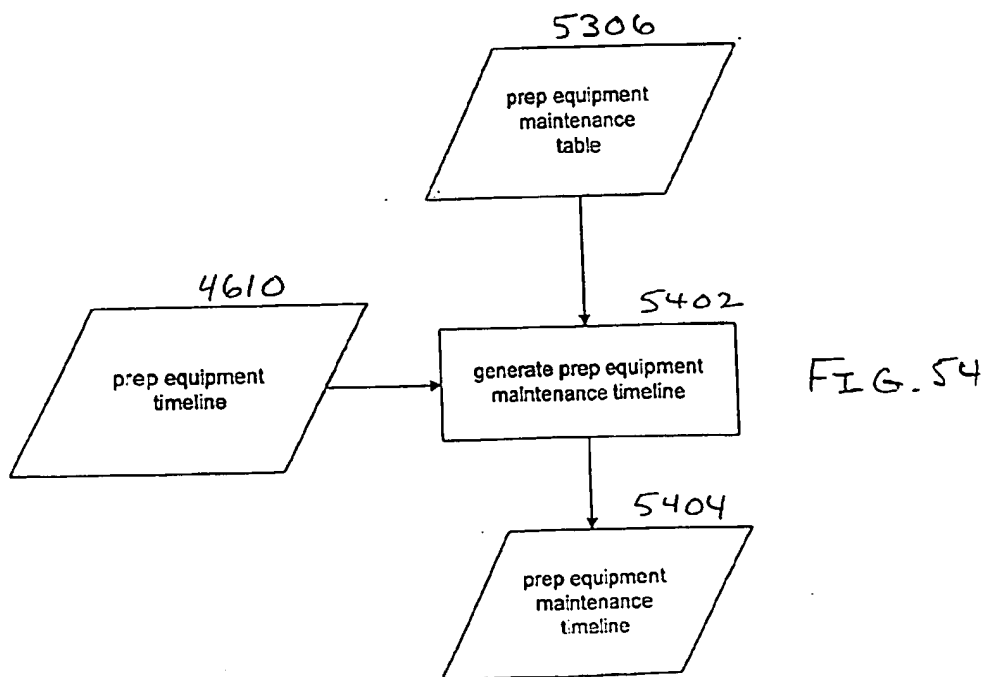
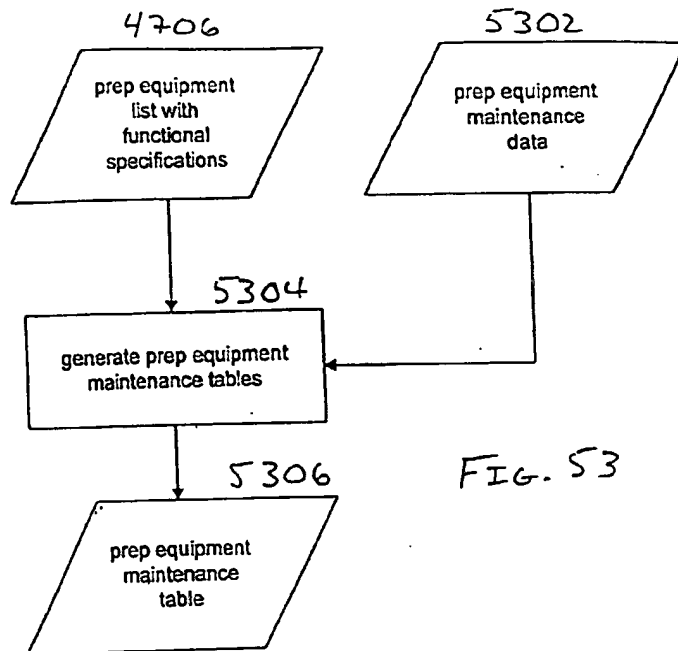
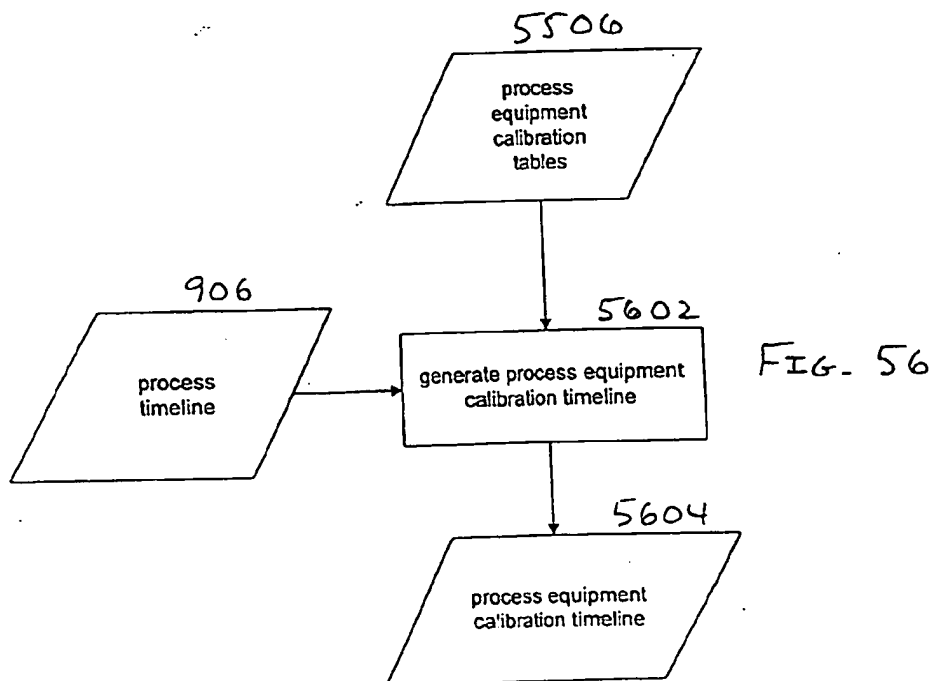
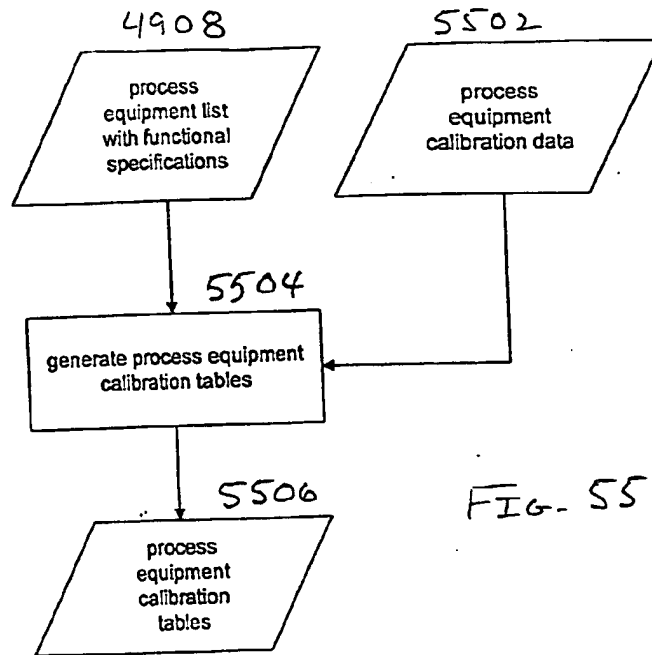


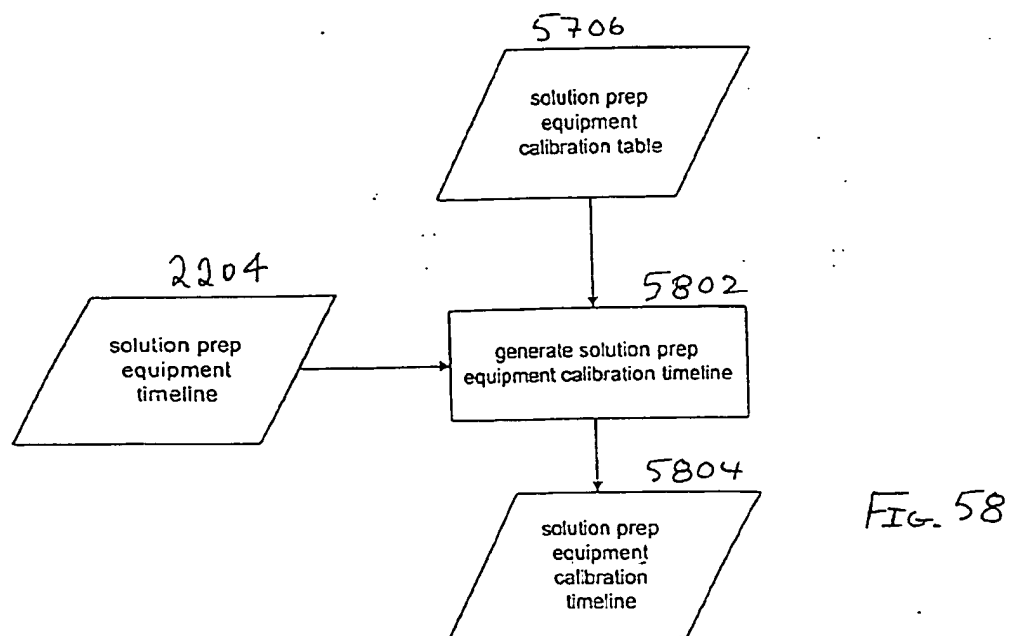
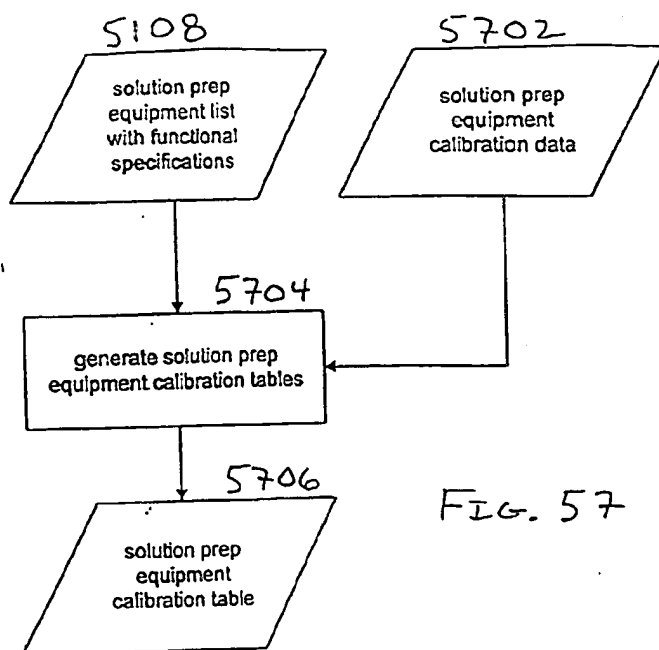
FIG. 48

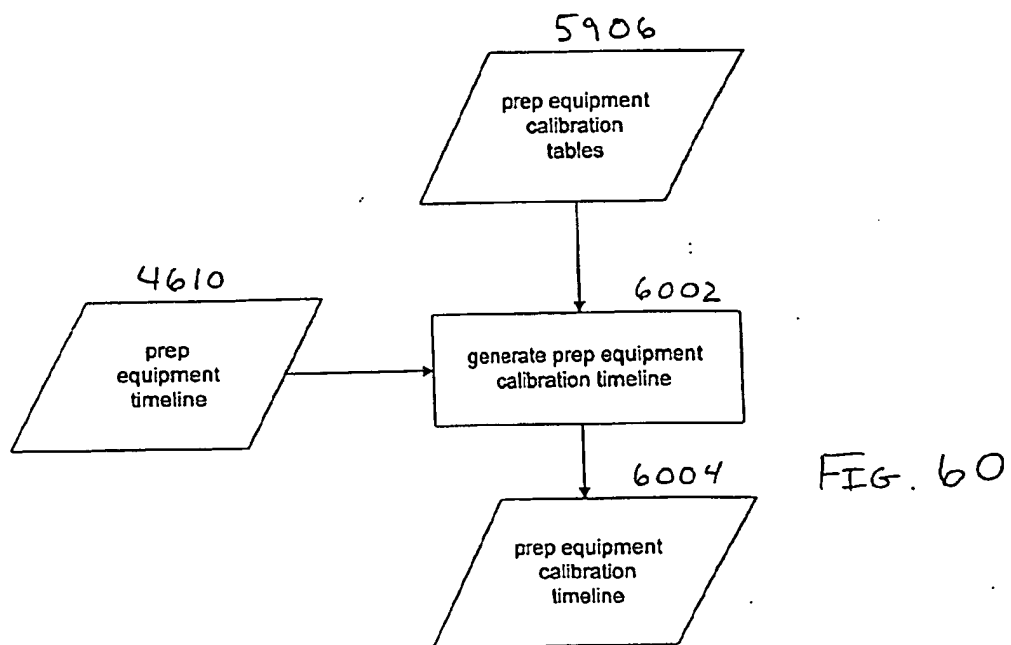
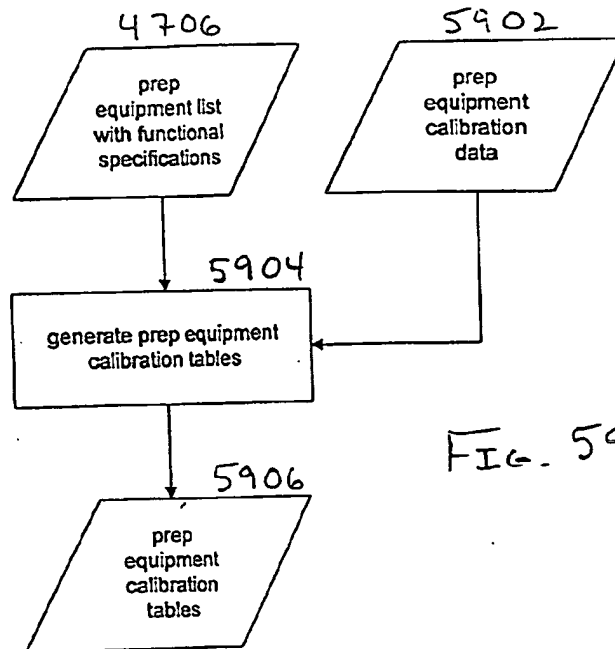


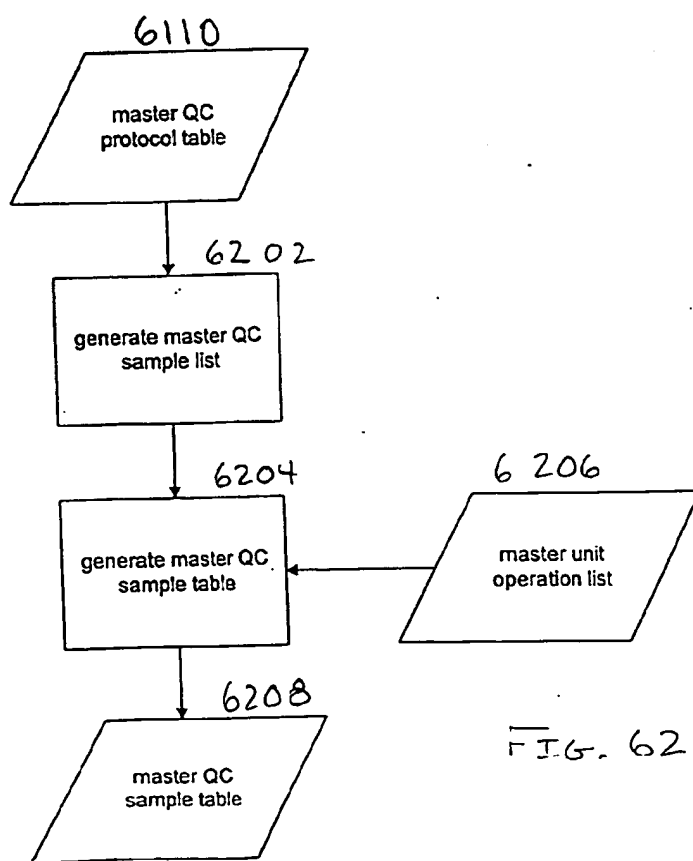
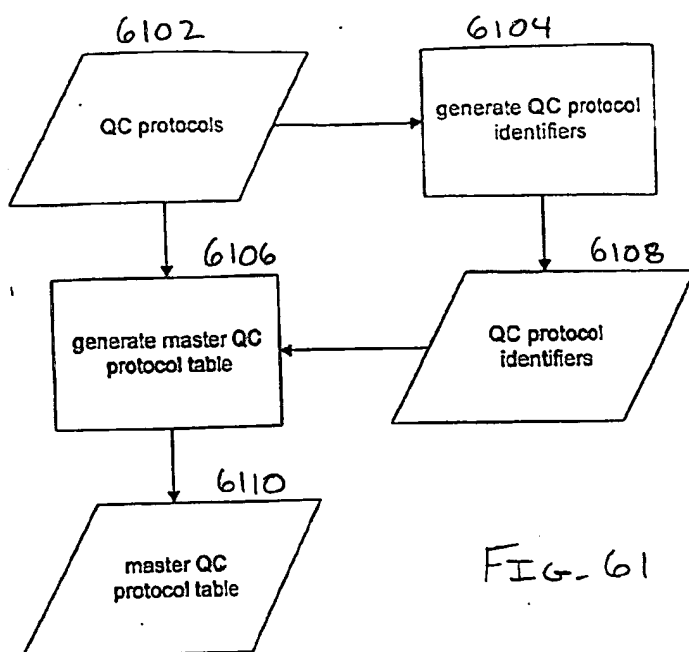


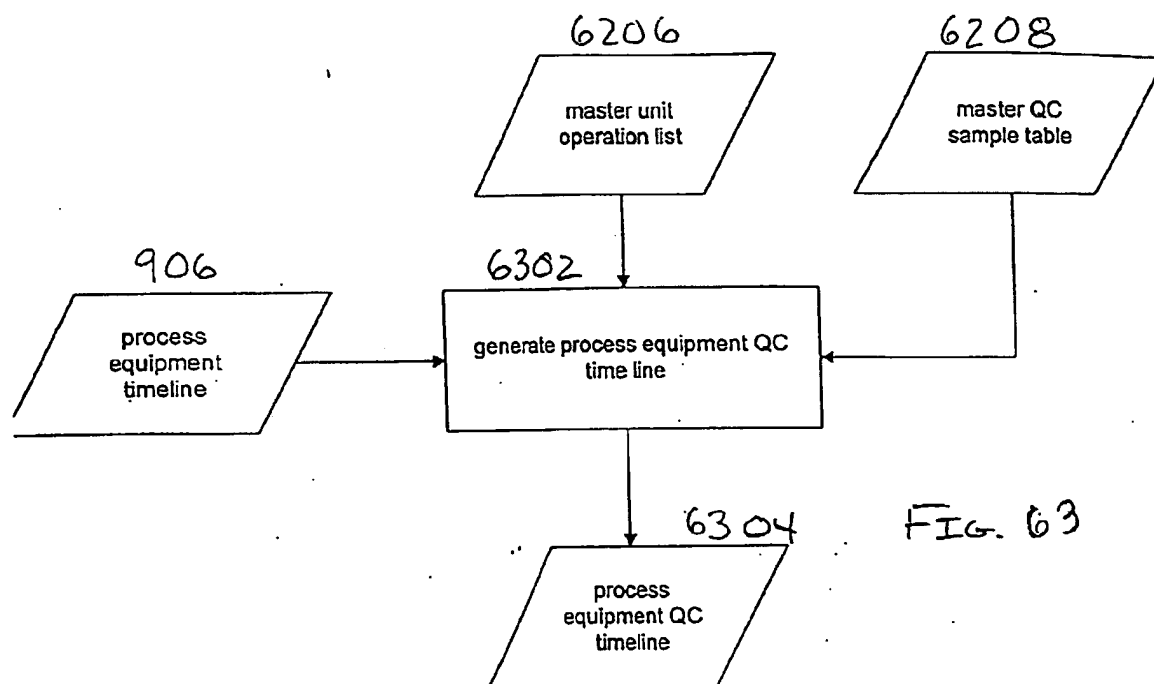












Equipment Maintenance Table - Microbial Fermentation

6402

6404

6406

6408

Equipment Items	Filters				Gaskets				Bearings			
	Materials		Labor		Materials		Labor		Materials		Labor	
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours
40 C Stock Freezer												
Shaking Water Bath												
Floor Incubator-Shaker												
Microscope												
Seed Bioreactor												
Production Bioreactor	1	100	55	.55	.5	.0875	4894	1	500	55	.11	1
Harvest Heat Exchanger							6259	1	350	85	.249	1
Harvest Vessel												
Agitator												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
Agitator												
MF Wash Vessel												
MF Regeneration Vessel												
MF Storage Vessel												

FIG. 64A

Equipment Maintenance Table - Microbial Fermentation

6408 / 6410 6412

Equipment Items	Seals						Belts					
	Labor			Materials			Labor			Materials		
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle
40 C Shock Freezer												
Shaking Water Bath												
Floor Incubator-Shaker												
Microscope												
Seed Bioreactor												
Production Bioreactor												
Harvest Heat Exchanger												
Harvest Vessel												
Agitator												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
Agitator												
MF Wash Vessel												
MF Regeneration Vessel												
MF Storage Vessel												

Fig. 64B

Equipment Maintenance Table - Microbial Fermentation
 6414 6416 6418

Equipment Items	Shafts						Lubricant					
	Labor			Materials			Labor			Materials		
	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Cycle Life
40 C Stock Freezer												
Shaking Water Bath												
Floor Incubator-Shaker												
Microscope												
Seed Bioreactor												
Production Bioreactor	500	25	.05	1	.035							
Harvest Heat Exchanger												
Harvest Vessel												
Agitator												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
Agitator												
MF Wash Vessel												
MF Regeneration Vessel												
MF Storage Vessel												

Fig. 64C

Equipment Maintenance Table - Microbial Fermentation

6420

6418

Equipment Items	Thermal Media									
	Labor					Materials				
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours
Microbial Fermentation										
-80 C Stock Freezer										
Shaking Water Bath										
Floor Incubator-Shaker										
Microscope										
Seed Bioreactor	1.5	.03	.5	.175						
Production Bioreactor					56258	5	500	.85	425	1
Harvest Heat Exchanger										
Harvest Vessel										
Agitator										
Pump										
Filter Holder										
Manifolding										
Instrumentation										
MF Flush Vessel										
MF Prime Vessel										
MF Filtrate Vessel										
Agitator										
MF Wash Vessel										
MF Regeneration Vessel										
MF Storage Vessel										

Fig. 64D

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Filters						Gaskets						Bearings	
	Materials			Labor			Materials			Labor			Materials	
	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	
MF Wash Vessel														
Pump														
Filter Holder														
Manifolding														
Instrumentation														
MF Flush Vessel														
MF Prime Vessel														
MF Filtrate Vessel														
MF Wash Vessel														
MF Regeneration Vessel														
MF Storage Vessel														
MF Cell Resuspension Vessel														
MF Reuspension Vessel														
Stir Plate														
Cell Disruptor														
Lysate Vessel														
MF Cell Resuspension Vessel														
MF Reuspension Vessel														
Stir Plate														
MF Wash Vessel														
Pump														
Filter Holder														

FIG. 64E

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Seals						Belts					
	Labor			Materials			Labor			Materials		
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.
MF Wash Vessel												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
MF Wash Vessel												
MF Regeneration Vessel												
MF Storage Vessel												
Resuspension Vessel												
Stir Plate												
Cell Disruptor												
Lysate Vessel												
Resuspension Vessel												
Stir Plate												
MF Wash Vessel												
Pump												
Filter Holder												

Fig. 64F

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shifts						Lubricant						
	Labor			Materials			Labor			Materials			
	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life
MF Wash Vessel													
Pump													
Filter Holder													
Manifolding													
Instrumentation													
MF Flush Vessel													
MF Prime Vessel													
MF Filtrate Vessel													
MF Wash Vessel													
MF Regeneration Vessel													
MF Storage Vessel													
Resuspension Vessel													
Stir Plate													
Cell Disruptor													
Lysate Vessel													
Resuspension Vessel													
Stir Plate													
MF Wash Vessel													
Pump													
Filter Holder													

Fig. 64G

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Thermal Media									
	Labor					Materials				
	Unit Cost	\$/Cyclo	Hours	\$/Cyclo	Item No.	Qty	Cycle Life	Unit Cost	\$/Cyclo	Hours
MF Wash Vessel										
Pump										
Filter Holder										
Manifolding										
Instrumentation										
MF Flush Vessel										
MF Prime Vessel										
MF Filtrate Vessel										
MF Wash Vessel										
MF Regeneration Vessel										
MF Storage Vessel										
Resuspension Vessel										
Stir Plate										
Cell Disruptor										
Lysate Vessel										
Resuspension Vessel										
Stir Plate										
MF Wash Vessel										
Pump										
Filter Holder										

Fig. 644

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Seals						Belts								
	Labor			Materials			Labor			Materials					
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty
Manifolding															
Instrumentation															
MF Flush Vessel															
MF Prime Vessel															
MF Filtrate Vessel															
MF Dilute Vessel															
MF Wash Vessel															
MF Regeneration Vessel															
MF Storage Vessel															
Renaturant Vessel															
Slit Plate															
Pump															
Filter Holder															
Manifolding															
Instrumentation															
UF Flush Vessel															
UF Prime Vessel															
UF Filtrate Vessel															
UF Wash Vessel															
UF Diluent Vessel															
UF Regeneration Vessel															
UF Storage Vessel															

FIG-64J

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shafts						Lubricant					
	Labor			Materials			Labor			Materials		
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty
Manifolding Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
MF Dilute Vessel												
MF Wash Vessel												
MF Regeneration Vessel												
MF Storage Vessel												
Renaturation Vessel												
Stir Plate												
Pump												
Filter Holder												
Manifolding Instrumentation												
UF Flush Vessel												
UF Prime Vessel												
UF Filtrate Vessel												
UF Wash Vessel												
UF Diluent Vessel												
UF Regeneration Vessel												
UF Storage Vessel												

Fig. 64 K

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Thermal Media										
	Labor			Materials				Labor			
	Unit Cost	\$/Cyclo	Hours	\$/Cyclo	Item No.	Qty	Cycle Life	Unit Cost	\$/Cyclo	Hours	\$/Cyclo
Manifolding Instrumentation											
MF Flush Vessel											
MF Prime Vessel											
MF Filtrate Vessel											
MF Dilute Vessel											
MF Wash Vessel											
MF Regeneration Vessel											
MF Storage Vessel											
Renaturant Vessel											
Stir Plato											
Pump											
Filter Holder											
Manifolding Instrumentation											
UF Flush Vessel											
UF Prime Vessel											
UF Filtrate Vessel											
UF Wash Vessel											
UF Diluent Vessel											
UF Regeneration Vessel											
UF Storage Vessel											

FIG. 64L

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Filters						Gaskets						Bearings					
	Materials			Labor			Materials			Labor			Materials			Labor		
	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours
UF Waste Vessel																		
Chromatography Column																		
Pump																		
Inst. & Control System																		
Manifolding																		
Equilibration Vessel																		
Wash Vessel																		
Eluent Vessel																		
Regenerate Vessel																		
Storage Vessel																		
Waste Vessel (1)																		
Product Vessel																		
Waste Vessel (2)																		
Chromatography Column																		
Pump																		
Inst. & Control System																		
Manifolding																		
Equilibration Vessel																		
Wash Vessel																		
Eluent Vessel																		
Regenerate Vessel																		

FIG. 64h

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Seals						Belts					
	Labor			Materials			Labor			Materials		
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.
UF Waste Vessel												
Chromatography Column												
Pump												
Inst. & Control System												
Manifolding												
Equilibration Vessel												
Wash Vessel												
Eluent Vessel												
Regenerate Vessel												
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
Chromatography Column												
Pump												
Inst. & Control System												
Manifolding												
Equilibration Vessel												
Wash Vessel												
Eluent Vessel												
Regenerate Vessel												

FIG. 64N

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shafts						Lubricant					
	Labor			Materials			Labor			Materials		
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty
UF Waste Vessel												
Regeneration Chromatography Column												
Pump												
Inst. & Control System												
Manifolding												
Equilibration Vessel												
Wash Vessel												
Eluent Vessel												
Regeneration Vessel												
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
Regeneration Chromatography Column												
Pump												
Inst. & Control System												
Manifolding												
Equilibration Vessel												
Wash Vessel												
Eluent Vessel												
Regeneration Vessel												

FIG. 640

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Thermal Media									
	Labor					Materials				
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours
UF Waste Vessel										
Chromatography Column										
Pump										
Inst. & Control System										
Manifolding										
Equilibration Vessel										
Wash Vessel										
Eluent Vessel										
Regenerate Vessel										
Storage Vessel										
Waste Vessel (1)										
Product Vessel										
Waste Vessel (2)										
Chromatography Column										
Pump										
Inst. & Control System										
Manifolding										
Equilibration Vessel										
Wash Vessel										
Eluent Vessel										
Regenerate Vessel										

FIG. 64P

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Filters						Gaskets						Bearings	
	Materials			Labor			Materials			Labor			Materials	
	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Item No.
Storage Vessel														
Waste Vessel (1)														
Product Vessel														
Waste Vessel (2)														
Recycle Vessel														
Pump														
Filter Holder														
Manifolding														
Instrumentation														
UF Flush Vessel														
UF Prime Vessel														
UF Filtrate Vessel														
UF Wash Vessel														
UF Diluent Vessel														
UF Regeneration Vessel														
UF Storage Vessel														
UF Waste Vessel														
Chromatography Column														
Pump														
Inst. & Control System														
Manifolding														
Equilibration Vessel														

FIG. 64Q

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shafts						Lubricant					
	Labor			Materials			Labor			Materials		
	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
Computer/Chromatography Column												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
UF Flush Vessel												
UF Prime Vessel												
UF Filtrate Vessel												
UF Wash Vessel												
UF Diluent Vessel												
UF Regeneration Vessel												
UF Storage Vessel												
UF Waste Vessel												
Chromatography Column												
Pump												
Inst. & Control System												
Manifolding												
Equilibration Vessel												

FIG. 64S

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Thermal Media									
	Labor		Materials		Labor		Materials		Labor	
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Unit Cost	\$/Cycle	Hours	\$/Cycle	Unit Cost	\$/Cycle
Storage Vessel										
Waste Vessel (1)										
Product Vessel										
Waste Vessel (2)										
Pump										
Filter Holder										
Manifolding										
Instrumentation										
UF Flush Vessel										
UF Prime Vessel										
UF Filtrate Vessel										
UF Wash Vessel										
UF Diluent Vessel										
UF Regeneration Vessel										
UF Storage Vessel										
UF Waste Vessel										
Chromatography Column										
Pump										
Inst. & Control System										
Manifolding										
Equilibration Vessel										

FIG. 64T

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Filters						Gaskets						Bearings					
	Materials			Labor			Materials			Labor			Materials			Labor		
	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours
Wash Vessel																		
Eluent Vessel																		
Regenerate Vessel																		
Storage Vessel																		
Waste Vessel (1)																		
Product Vessel																		
Waste Vessel (2)																		
Extraction Vessel																		
Pump																		
Filter Holder																		
Manifolding																		
Instrumentation																		
UF Flush Vessel																		
UF Prime Vessel																		
UF Filtrate Vessel																		
UF Wash Vessel																		
UF Diluent Vessel																		
UF Regeneration Vessel																		
UF Storage Vessel																		
UF Waste Vessel																		
Chromatography Column																		
Pump																		

FIG. 64U

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Seals						Belts					
	Labor			Materials			Labor			Materials		
	Qty	Cycle Lifo	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Lifo	Unit Cost	\$/Cycle	Item No.
Wash Vessel												
Eluent Vessel												
Regenerate Vessel												
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
Exchanger												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
UF Flush Vessel												
UF Prime Vessel												
UF Filtrate Vessel												
UF Wash Vessel												
UF Diluent Vessel												
UF Regeneration Vessel												
UF Storage Vessel												
UF Waste Vessel												
Chromatography Column												
Pump												

FIG. 64V

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shafts						Lubricant					
	Labor			Materials			Labor			Materials		
	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle
Wash Vessel												
Eluent Vessel												
Regenerate Vessel												
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
UF Flush Vessel												
UF Prima Vessel												
UF Filtrate Vessel												
UF Wash Vessel												
UF Diluent Vessel												
UF Regeneration Vessel												
UF Storage Vessel												
UF Waste Vessel												
Chromatography Column												
Pump												

FIG. 64 W

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Thermal Media							
	Labor				Materials			
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost
Wash Vessel								
Eluent Vessel								
Regenerate Vessel								
Storage Vessel								
Waste Vessel (1)								
Product Vessel								
Waste Vessel (2)								
Pump								
Filler Holder								
Manifolding								
Instrumentation								
UF Flush Vessel								
UF Prima Vessel								
UF Filtrate Vessel								
UF Wash Vessel								
UF Diluent Vessel								
UF Regeneration Vessel								
UF Storage Vessel								
UF Waste Vessel								
Chromatography Column								
Pump								

FIG. 64X

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Filters						Gaskets						Bearings	
	Materials			Labor			Materials			Labor			Materials	
	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	\$/Cycle
Inst. & Control System														
Manifolding														
Equilibration Vessel														
Wash Vessel														
Eluent Vessel														
Regenerate Vessel														
Storage Vessel														
Waste Vessel (1)														
Product Vessel														
Waste Vessel (2)														
MF Wash Vessel														
Pump														
Filter Holder														
Manifolding														
Instrumentation														
MF Flush Vessel														
MF Prime Vessel														
MF Filtrate Vessel														
MF Wash Vessel														

FIG. 64Y

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Seals										Belts				
	Labor				Materials			Labor			Materials				
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty
Inst. & Control System															
Manifolding															
Equilibration Vessel															
Wash Vessel															
Eluent Vessel															
Regenerate Vessel															
Storage Vessel															
Waste Vessel (1)															
Product Vessel															
Waste Vessel (2)															
MF Wash Vessel															
Pump															
Filter Holder															
Manifolding															
Instrumentation															
MF Flush Vessel															
MF Prime Vessel															
MF Filtrate Vessel															
MF Wash Vessel															

Fig. 642

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shafts						Lubricant					
	Labor			Materials			Labor			Materials		
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty
Cycle Life												
Inst. & Control System												
Manifolding												
Equilibration Vessel												
Wash Vessel												
Eluent Vessel												
Regenerate Vessel												
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
MF Wash Vessel												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
MF Wash Vessel												

FIG. 64 AA

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Thermal Media					
	Labor			Materials		
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty
Inst. & Control System						
Manifolding Equilibration Vessel						
Wash Vessel						
Eluent Vessel						
Regenerate Vessel						
Storage Vessel						
Waste Vessel (1)						
Product Vessel						
Waste Vessel (2)						
MF Wash Vessel						
Pump						
Filter Holder						
Manifolding Instrumentation						
MF Flush Vessel						
MF Prime Vessel						
MF Filtrate Vessel						
MF Wash Vessel						

Fig. 64AB

FIG. 66

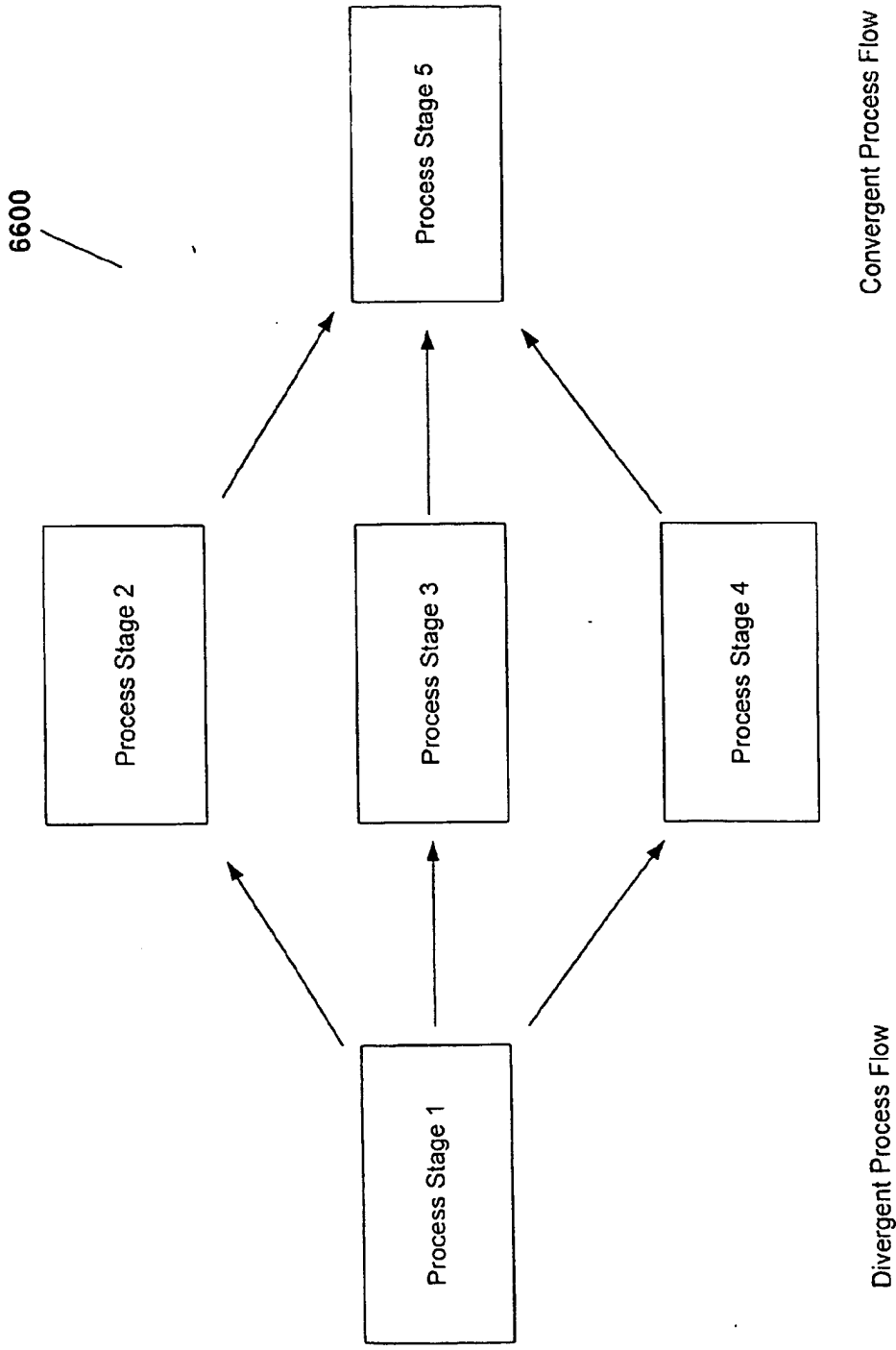


FIG. 67

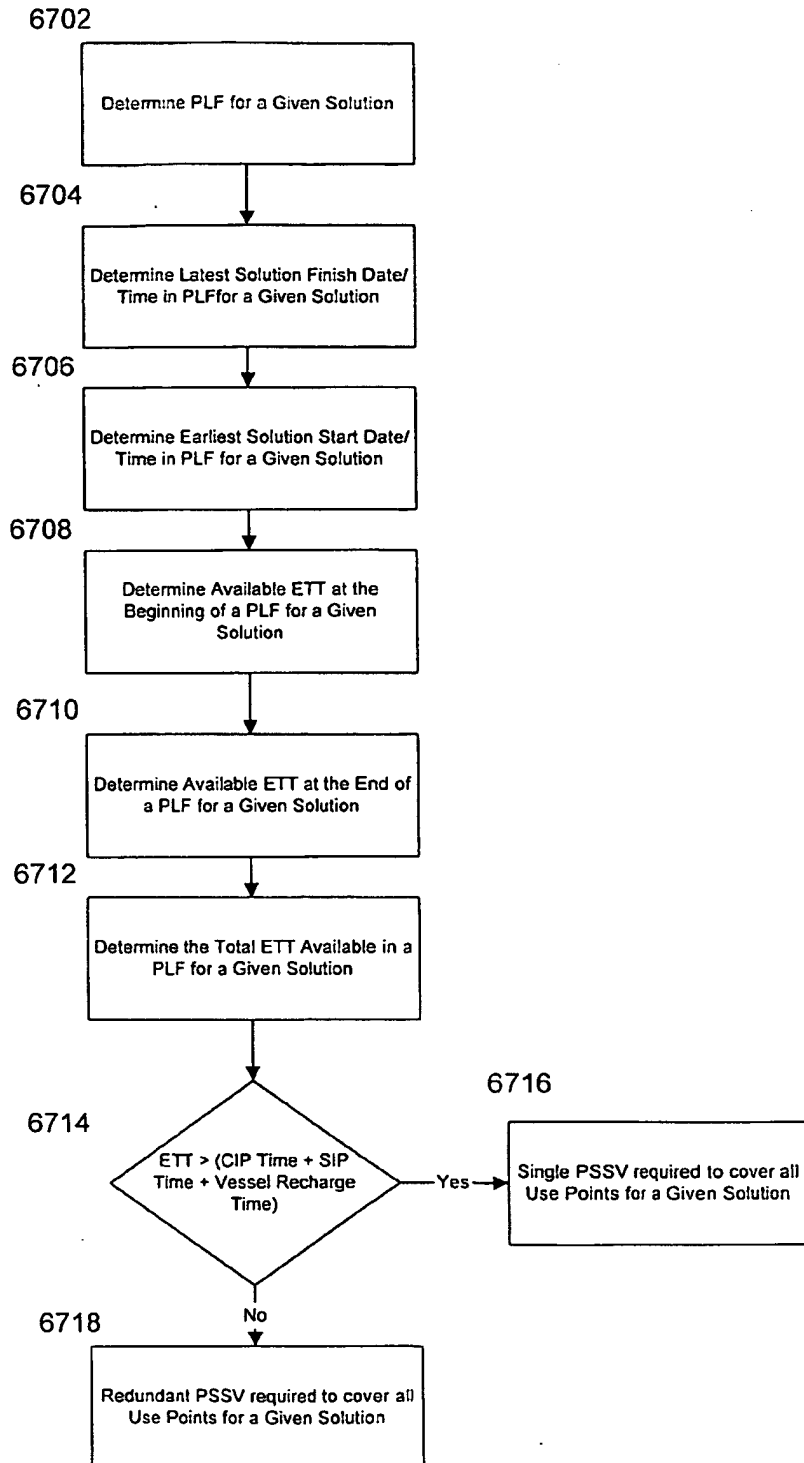


FIG. 68

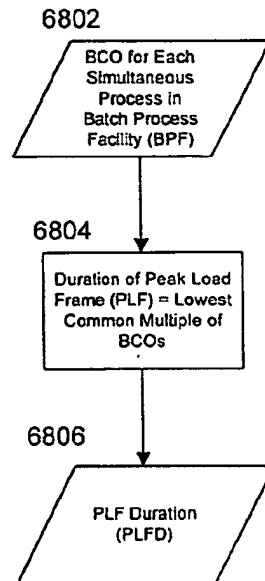
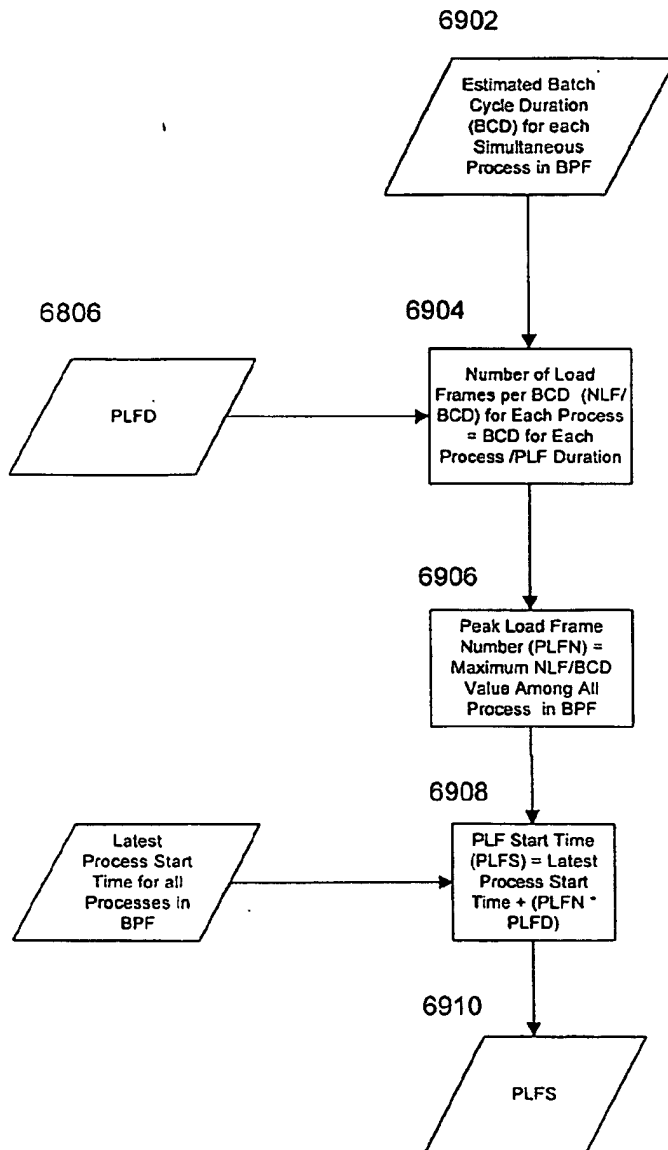


FIG. 69



[illegible]

Fig. 70

FIG. 72

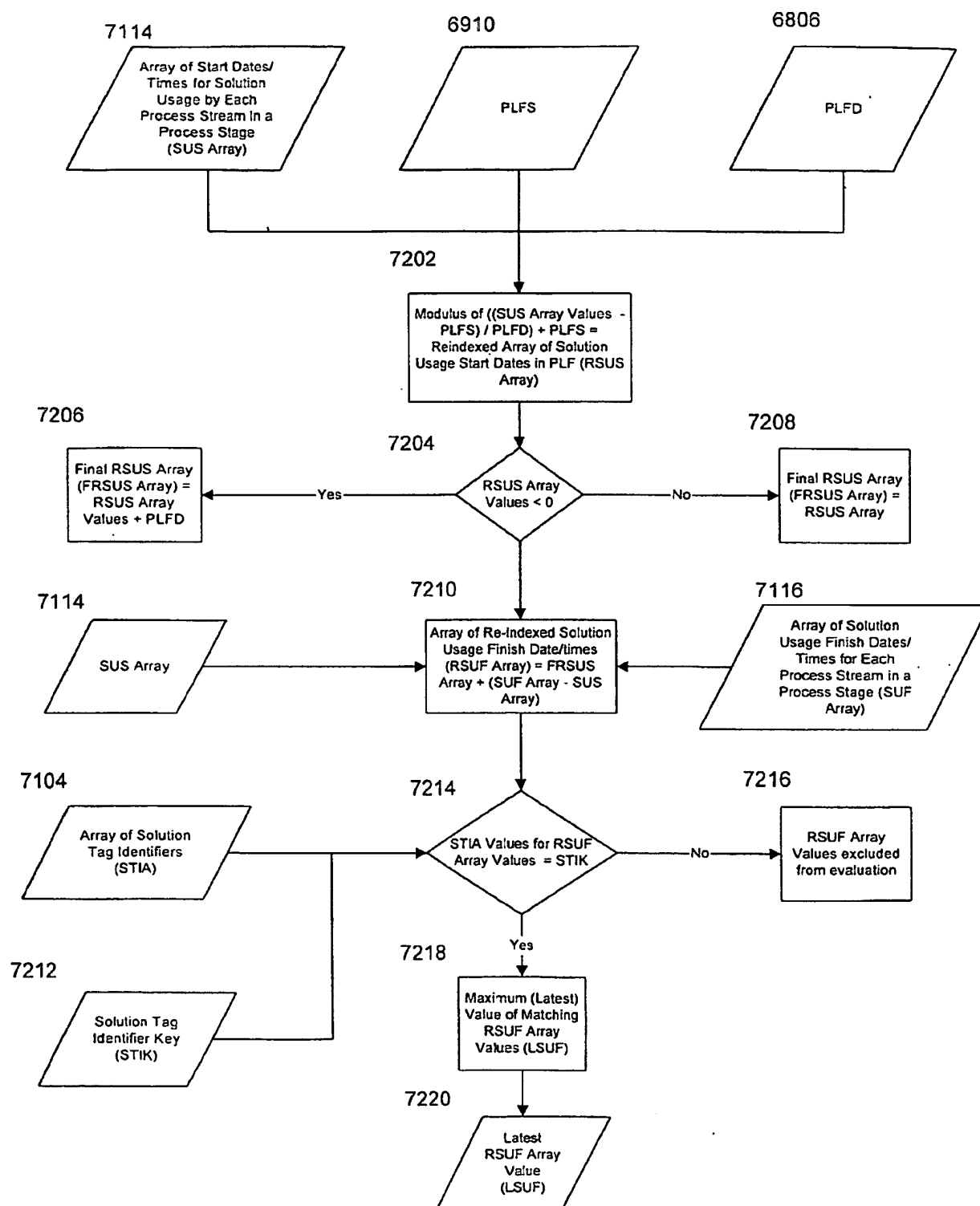


FIG. 73

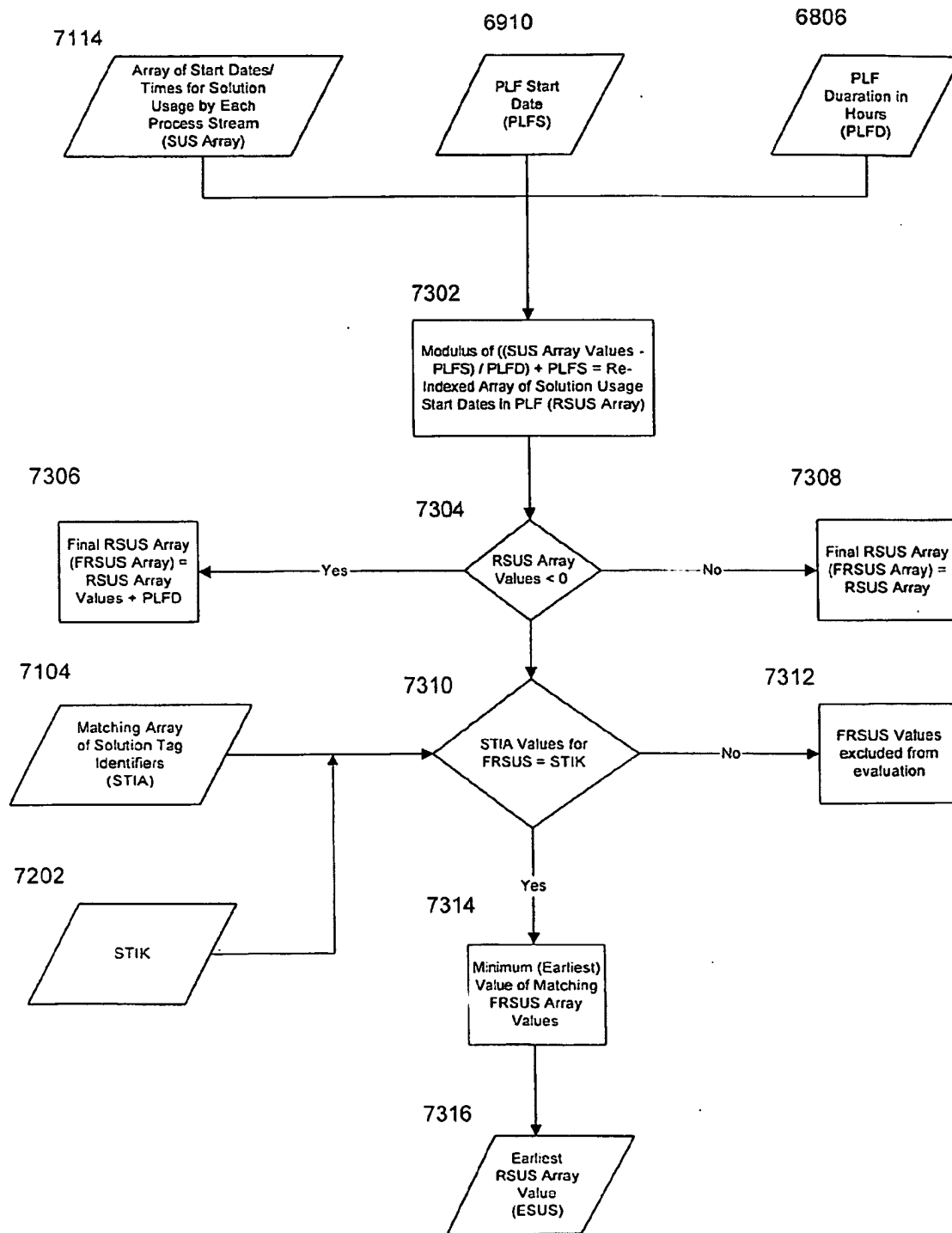


FIG. 74

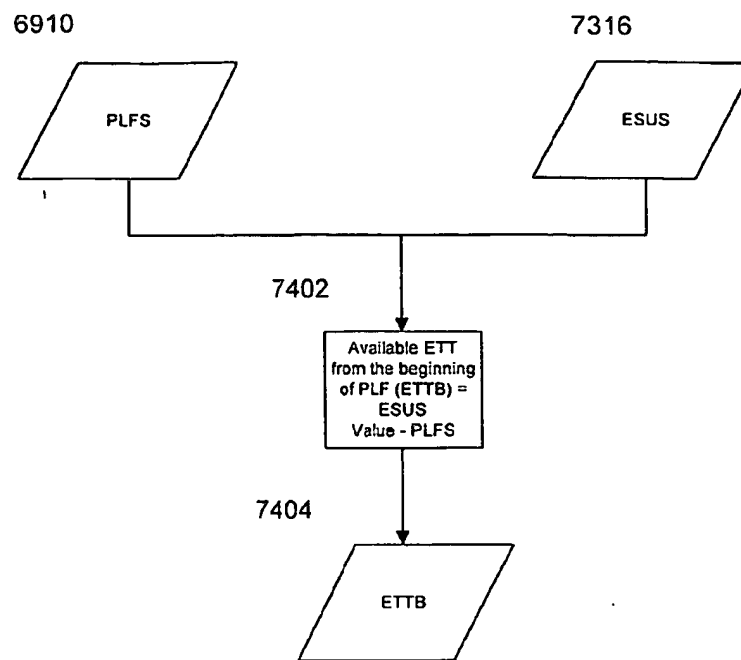


FIG. 75

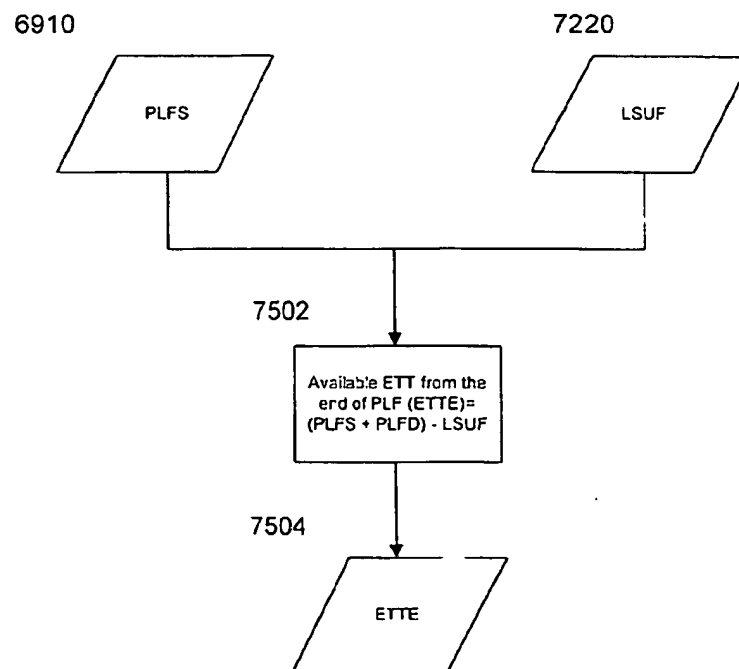


FIG. 76

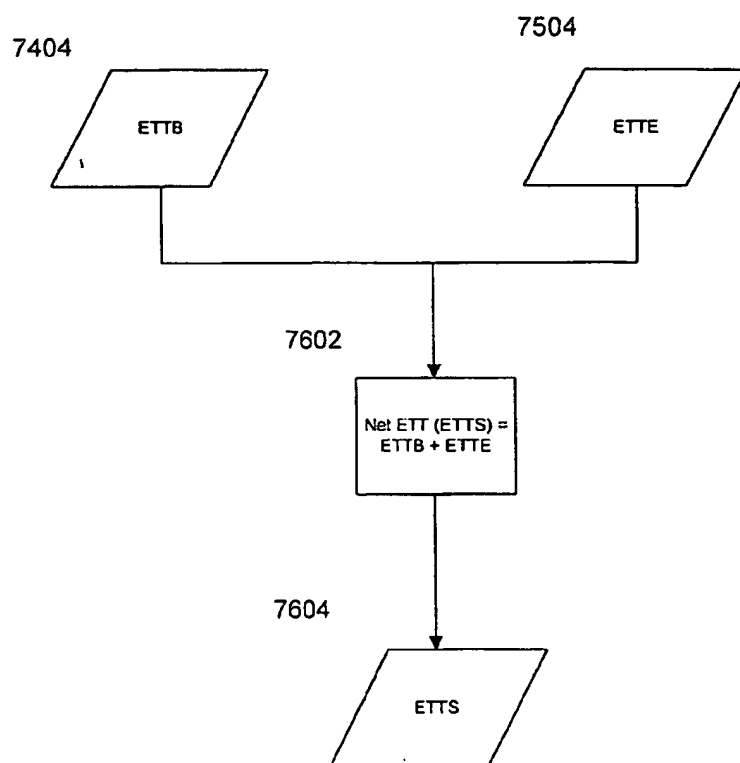


FIG. 77

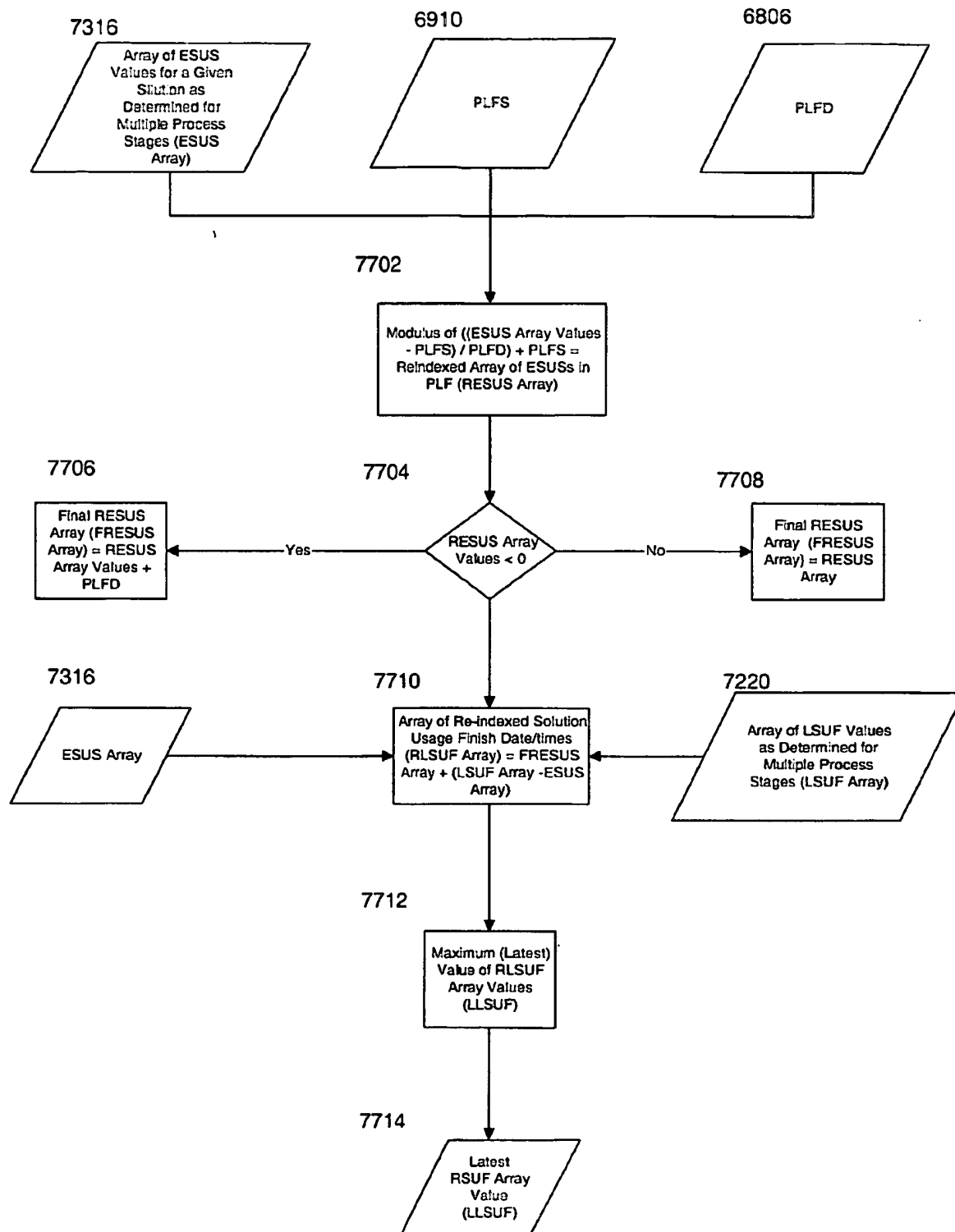


FIG. 78

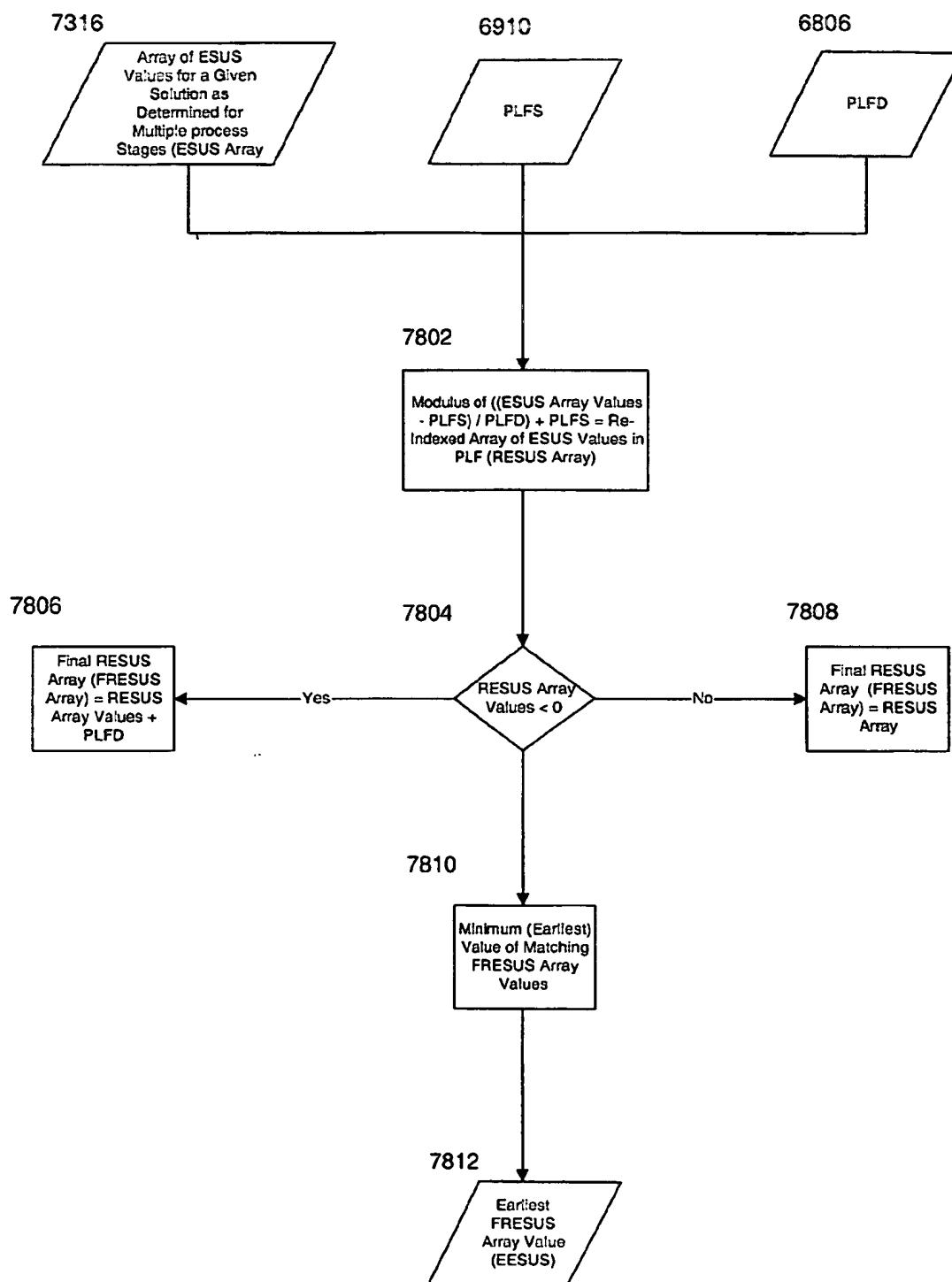


FIG. 79

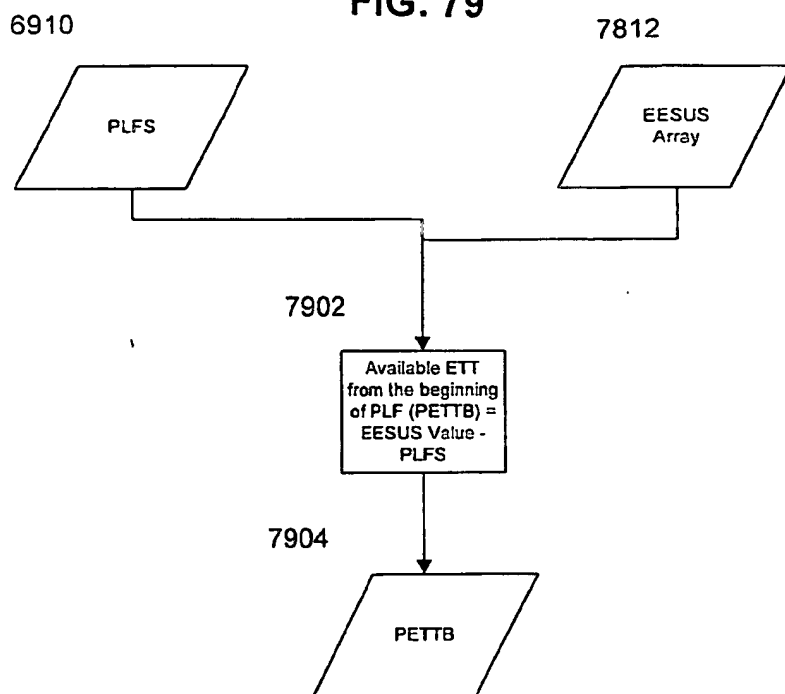


FIG. 80

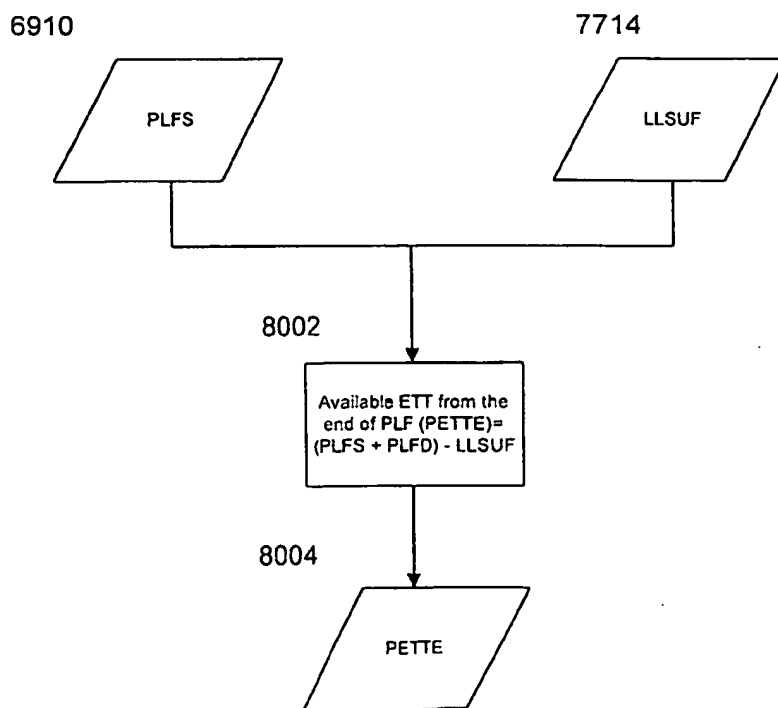
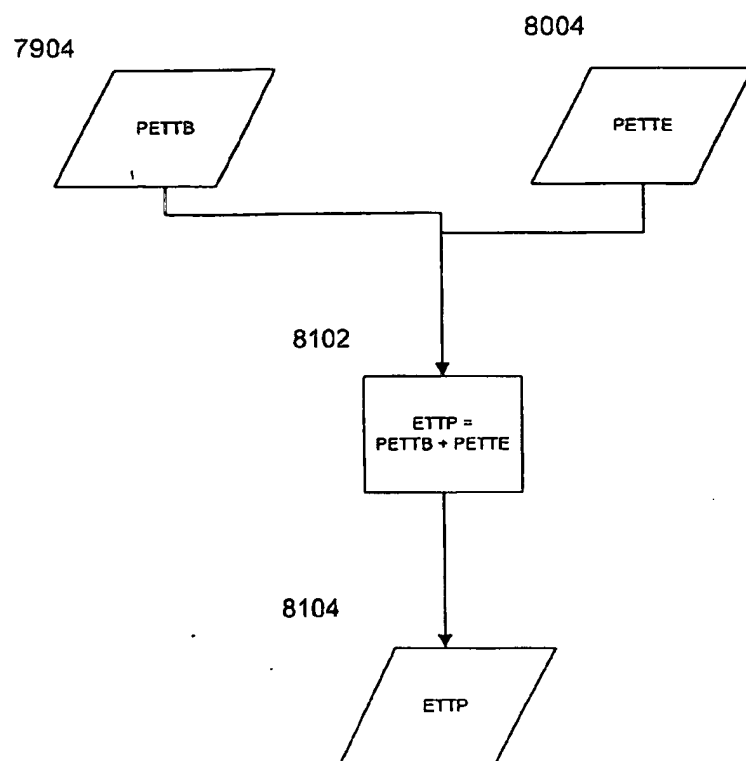


FIG. 81



UDP Seq. No.	Unit Operation Type	Process Design Cycles									
		Unit Op		Unit Op Cluster				Batch			
		Code	Offset (Hrs)	UnOp Start	UnOp End	Offset (Hrs)	UnOp Start	UnOp End	UnOp Start	UnOp End	Offset (Hrs)
1	68 STR - Suspension Production	1	0	1		0	1		1		0
2	74 Harvest/Feed - Suspension Production	3	24	1		0	20	2	2	4	72
3	34 Tangential Flow - Clarification	1	0	1		0	20	2	2	4	72
4	47 Dilution	1	0	1		0	20	2	2	4	72
5	99 End										

8202 8204 8206 8208 8210 8212 8214 8216 8218 8220 8222 8224 8226

FIG. 82

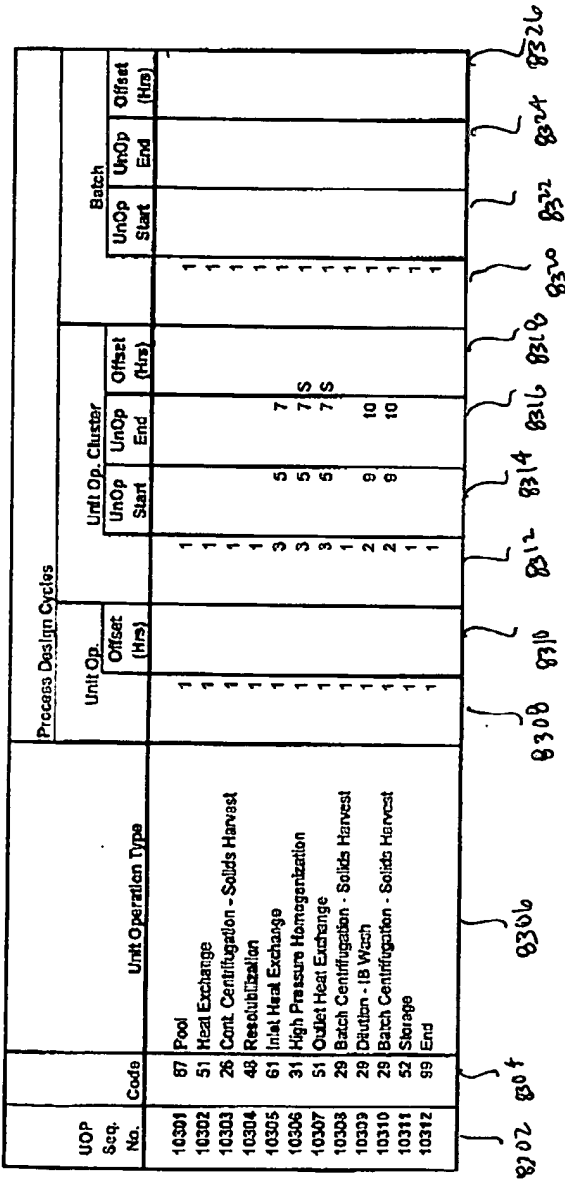


FIG. 83

FIG. 84A

8402 8404 8410 8412 8414 8416 8418 8420 8422 8424 8426 8428 8430 8432 8434 8436 8438 8440 8442 8444 8446 8448 8450 8452 8454 8456 8458 8460 8462 8464 8466 8468 8470 8472 8474 8476 8478 8480 8482 8484 8486 8488 8490 8492 8494 8496 8498 8500

Division	Location	Description	Present Flow Line										Proposed Flow Line										Future Flow Line										Future Flow Line										
			Capacity (GPM)		Flow (GPM)		Pressure (PSI)		Temperature (°F)		Velocity (FPS)		Pipe Size (in)		Material		Length (ft)		Cost (\$)		Notes		Date		By		Check		Date		By		Check		Date		By		Check				
			Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.	Calc.	Req.					
11.1.1	171	North-South Road																																									
		Source																																									
		20277.36 Lbs - 0.0 Lbs																																									
		0.0 Lbs																																									
		0.0 Lbs																																									
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		0.0 Lbs																																									

FIG. 9A-B

Operation	Description	Process Time (Min)										Start	End	Time
		Calc	Log	Adj	Prep	Exec	Comp	Start	End	Start	End			
CP	CP	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
SP	SP	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Source	Source	2.5	2.5	2.5	2.5	2.5	2.5	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
3.1.1	3.1.1 Homogeneous													
Set Up	Set Up	1.0	0.0	1.0	1.0	1.0	1.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Load	Load	2.5	0.0	2.5	2.5	2.5	2.5	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Wash	Wash	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
CP	CP	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
SP	SP	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Source	Source	2.5	2.5	2.5	2.5	2.5	2.5	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
3.1.2	3.1.2 Quasi-Homogeneous													
Set Up	Set Up	1.0	0.0	1.0	1.0	1.0	1.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Load	Load	2.5	0.0	2.5	2.5	2.5	2.5	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Wash	Wash	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
CP	CP	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
SP	SP	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Source	Source	2.5	2.5	2.5	2.5	2.5	2.5	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
3.1.3	3.1.3 Homogeneous													
Set Up	Set Up	1.0	0.0	1.0	1.0	1.0	1.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Load	Load	2.5	0.0	2.5	2.5	2.5	2.5	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Wash	Wash	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
CP	CP	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
SP	SP	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Source	Source	2.5	2.5	2.5	2.5	2.5	2.5	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
3.1.4	3.1.4 Quasi-Homogeneous													
Set Up	Set Up	1.0	0.0	1.0	1.0	1.0	1.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Load	Load	2.5	0.0	2.5	2.5	2.5	2.5	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Wash	Wash	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
CP	CP	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
SP	SP	0.0	0.0	0.0	0.0	0.0	0.0	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00
Source	Source	2.5	2.5	2.5	2.5	2.5	2.5	11.0	11.0	11.0	11.0	01:00:00	01:00:00	01:00:00

FIG. 84C

[illegible]

FIG. 84E

[illegible]

FIG. 85

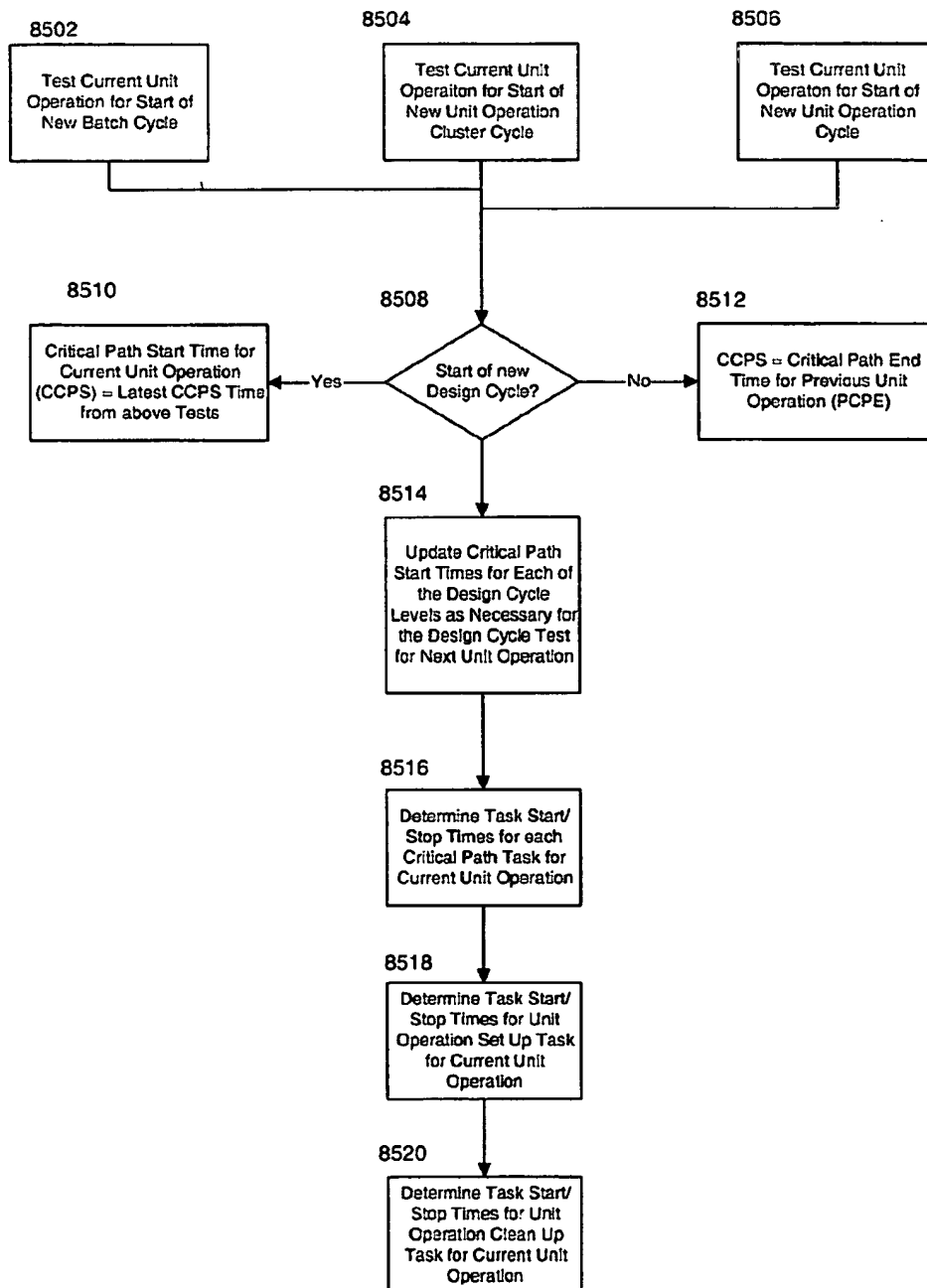


FIG. 86

8602

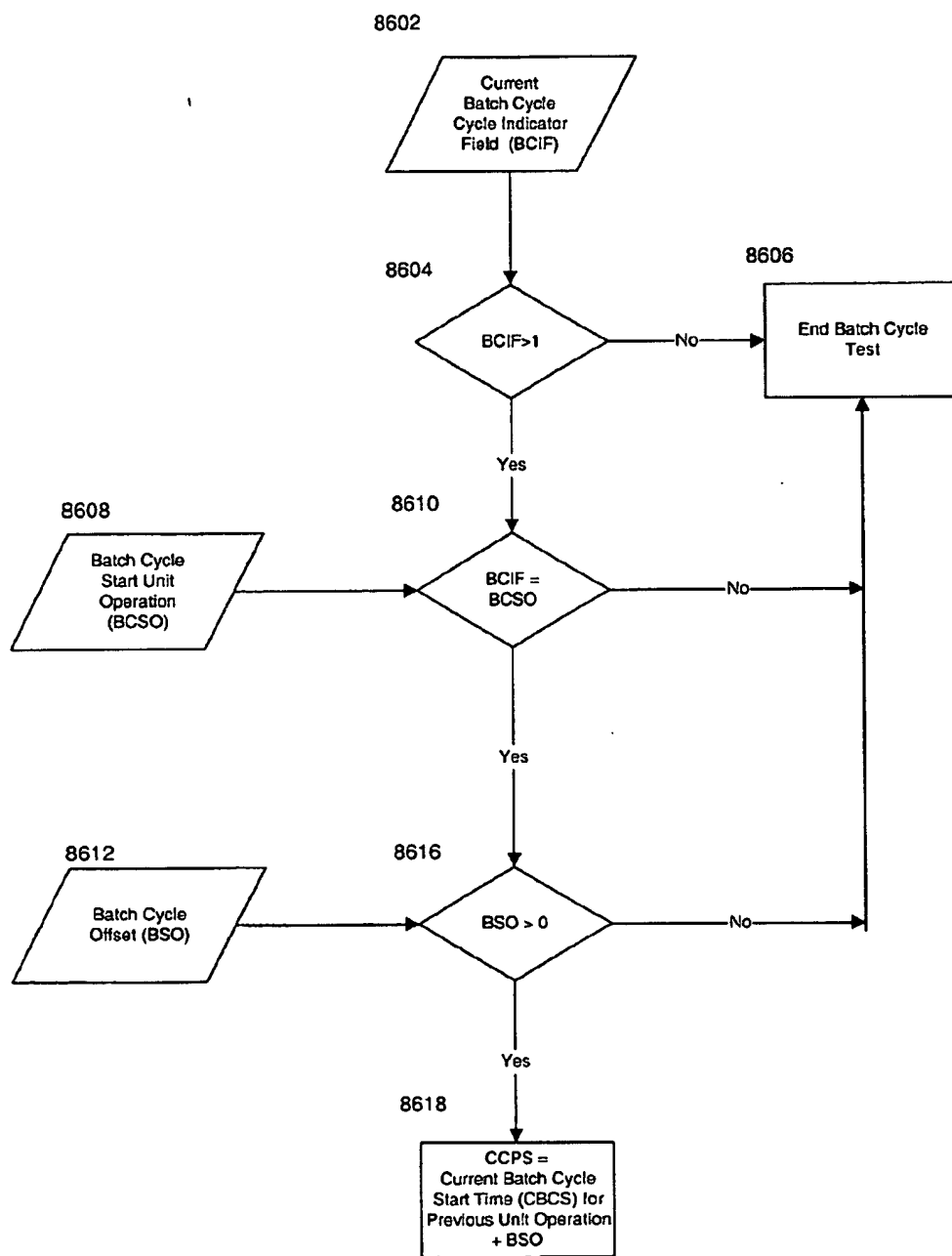


FIG. 87'

8704

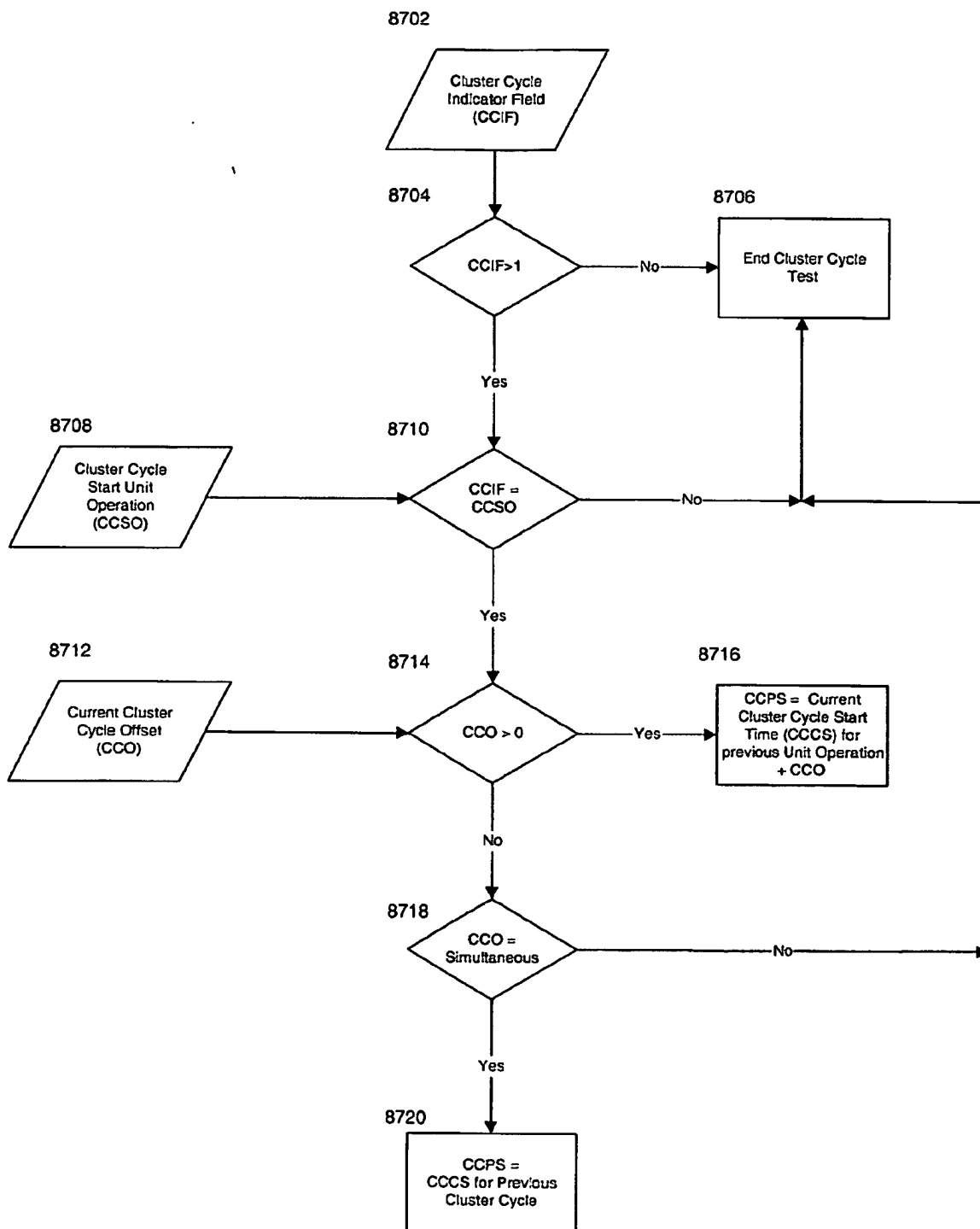


FIG. 88

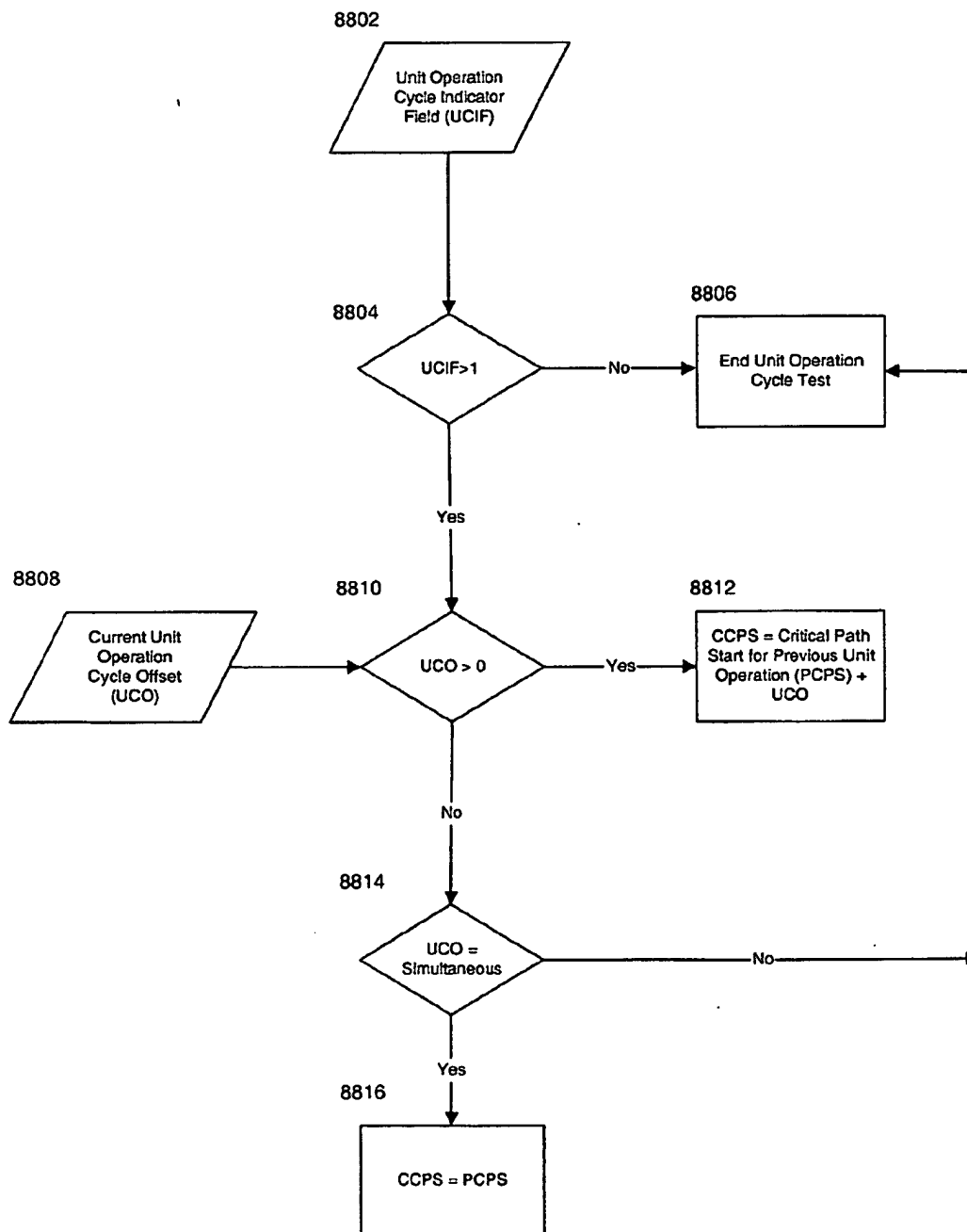
8806
J

FIG. 89

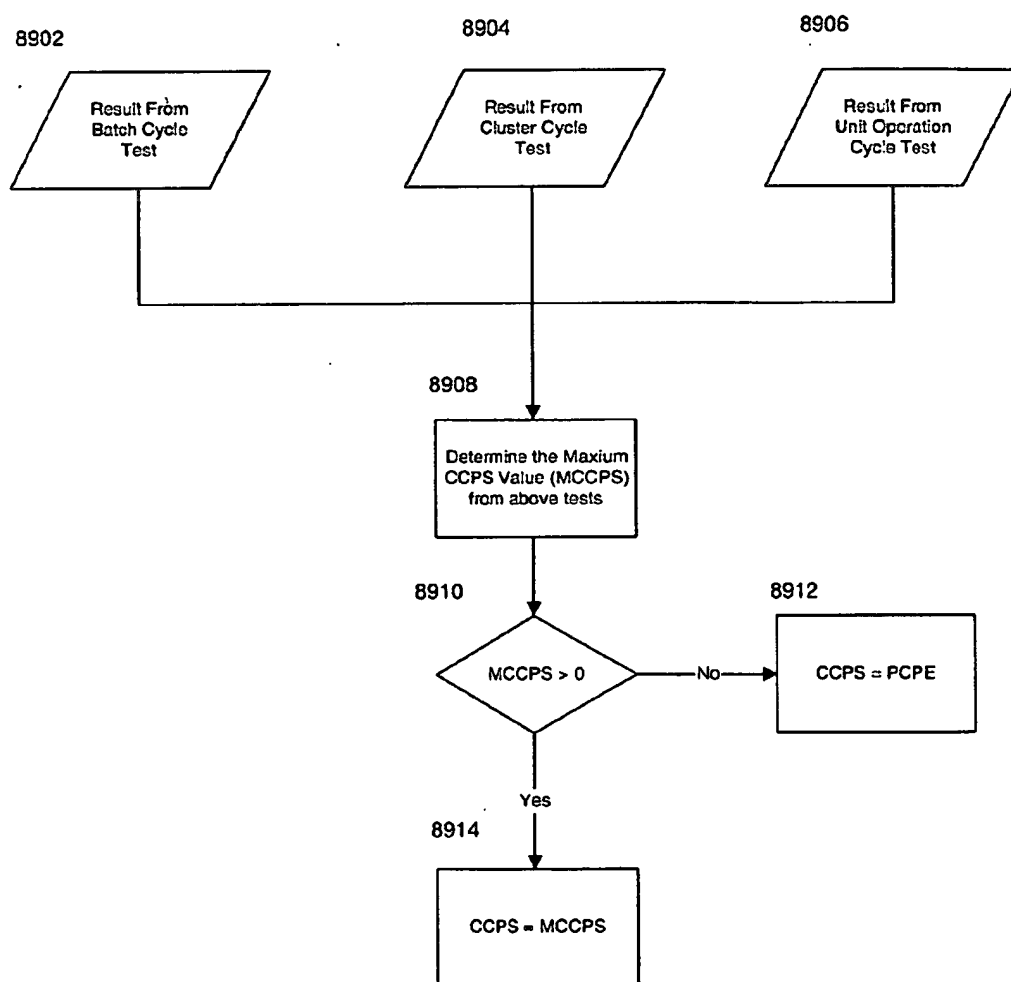


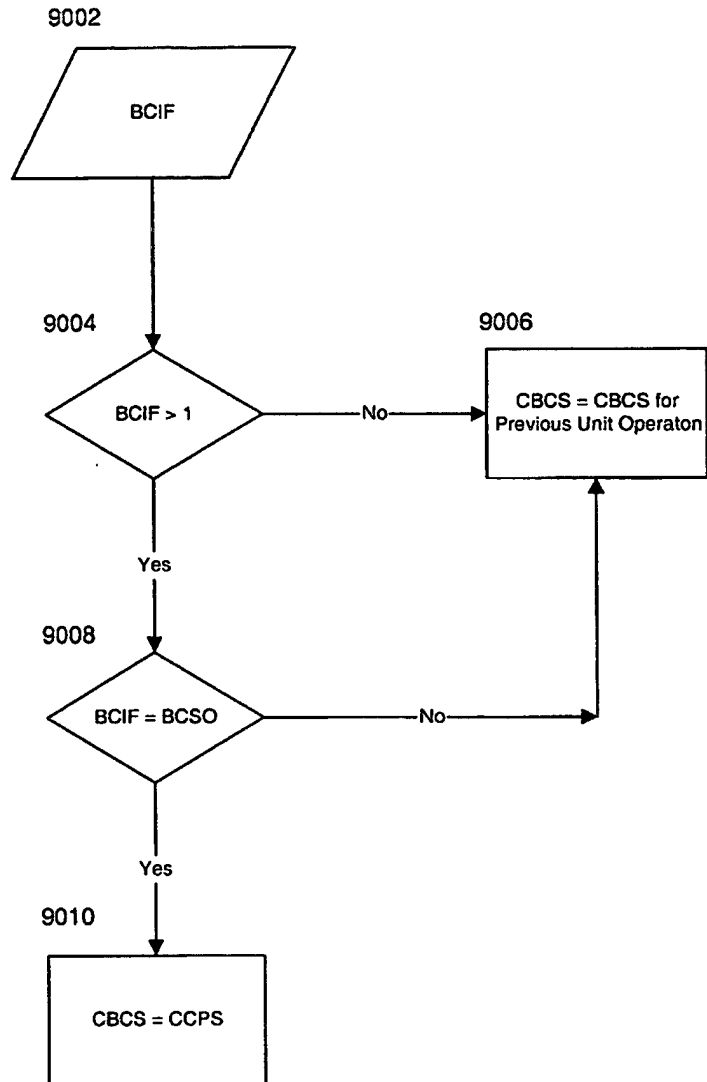
FIG. 90

FIG. 91

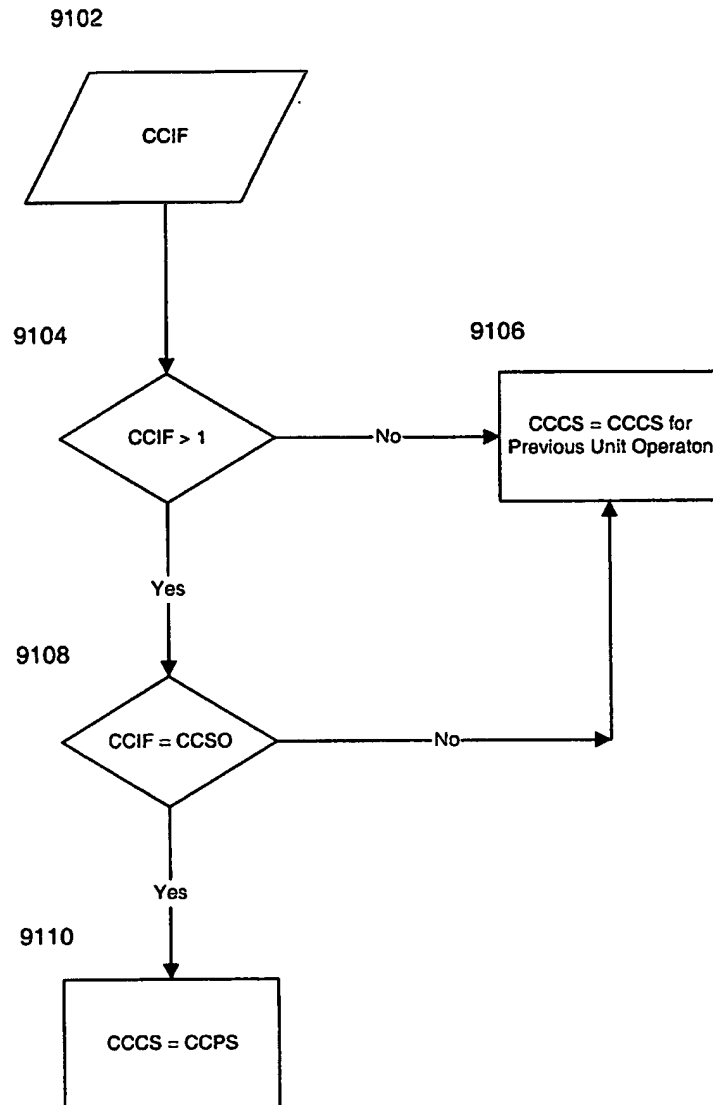


FIG. 92

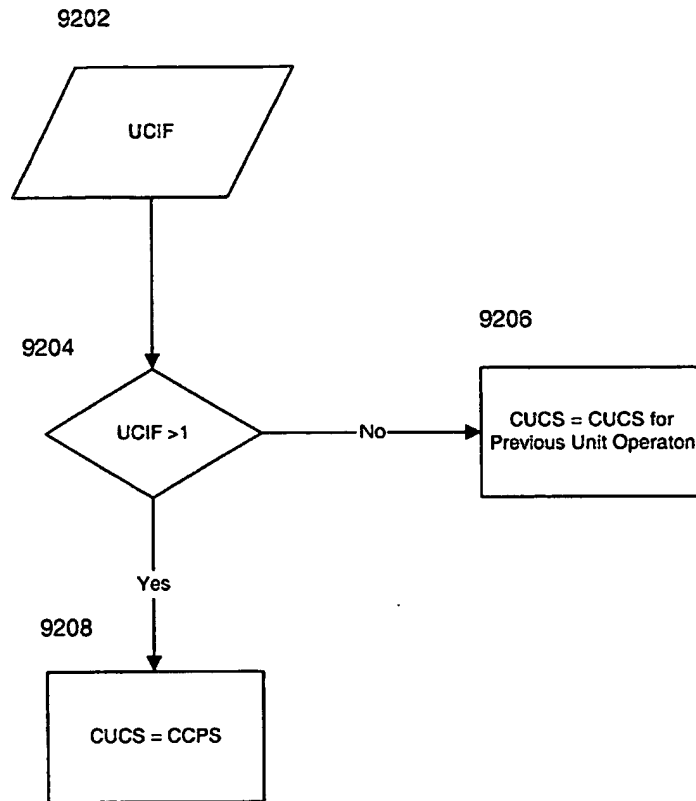


FIG. 93

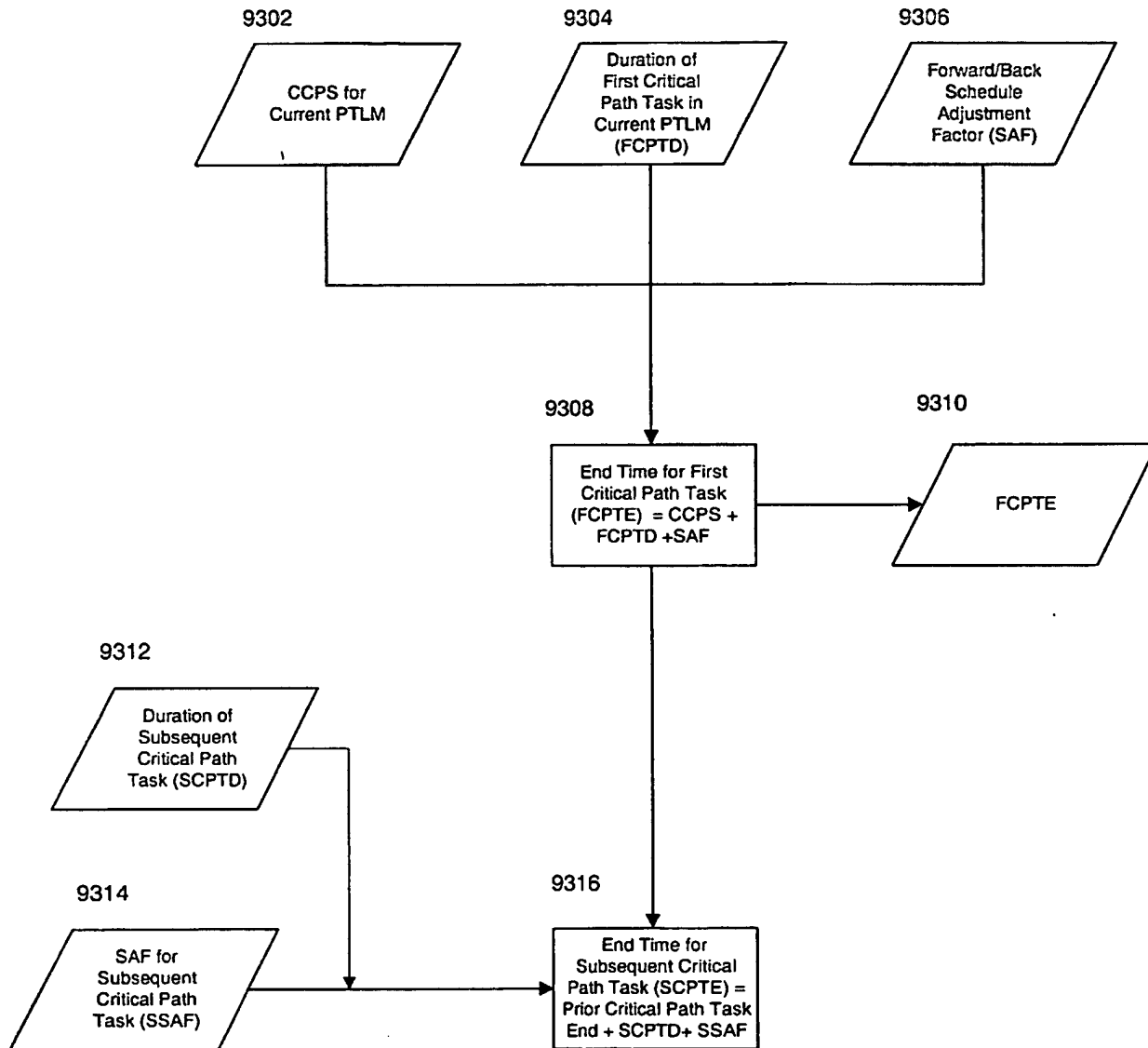


FIG. 94

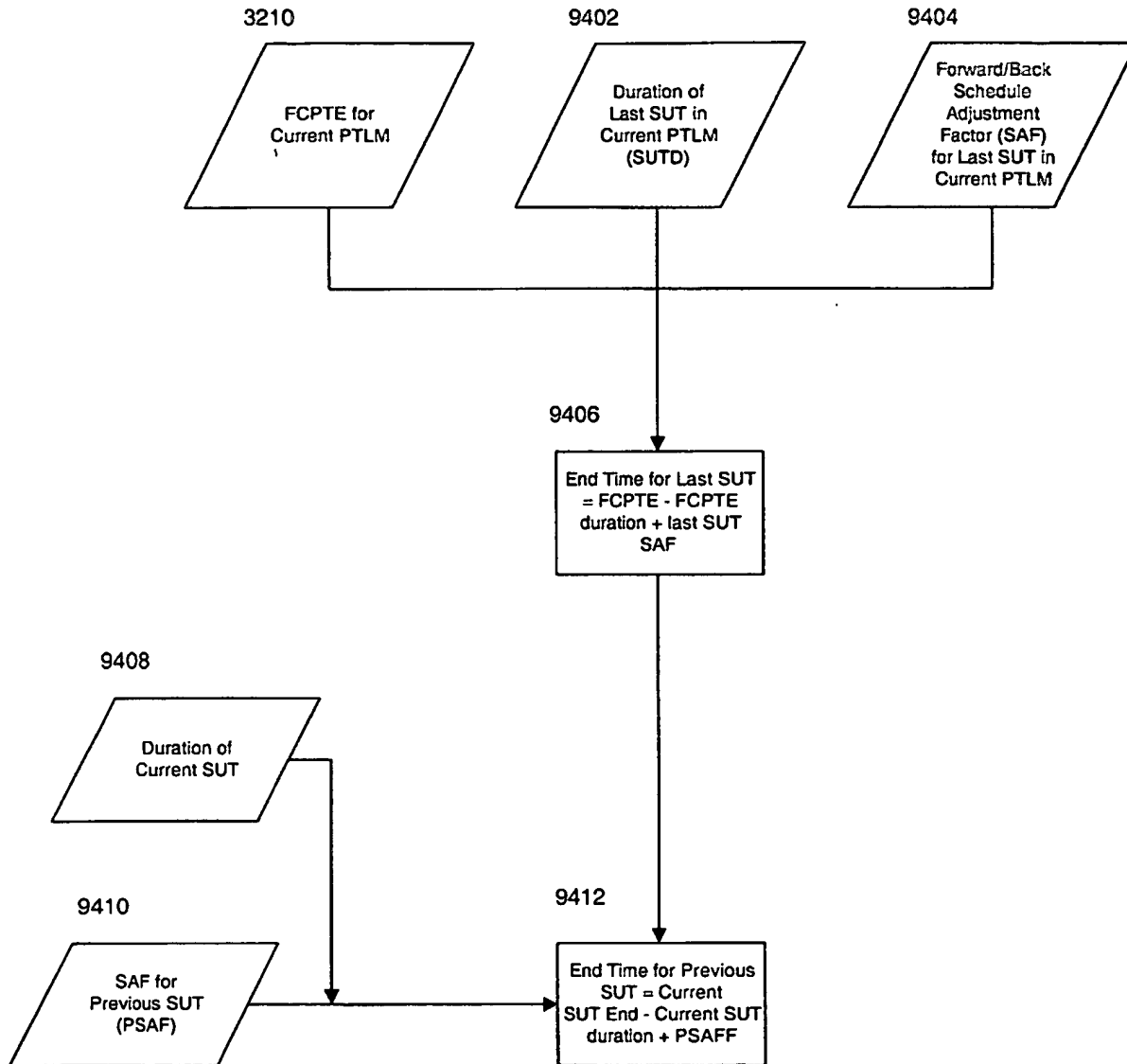
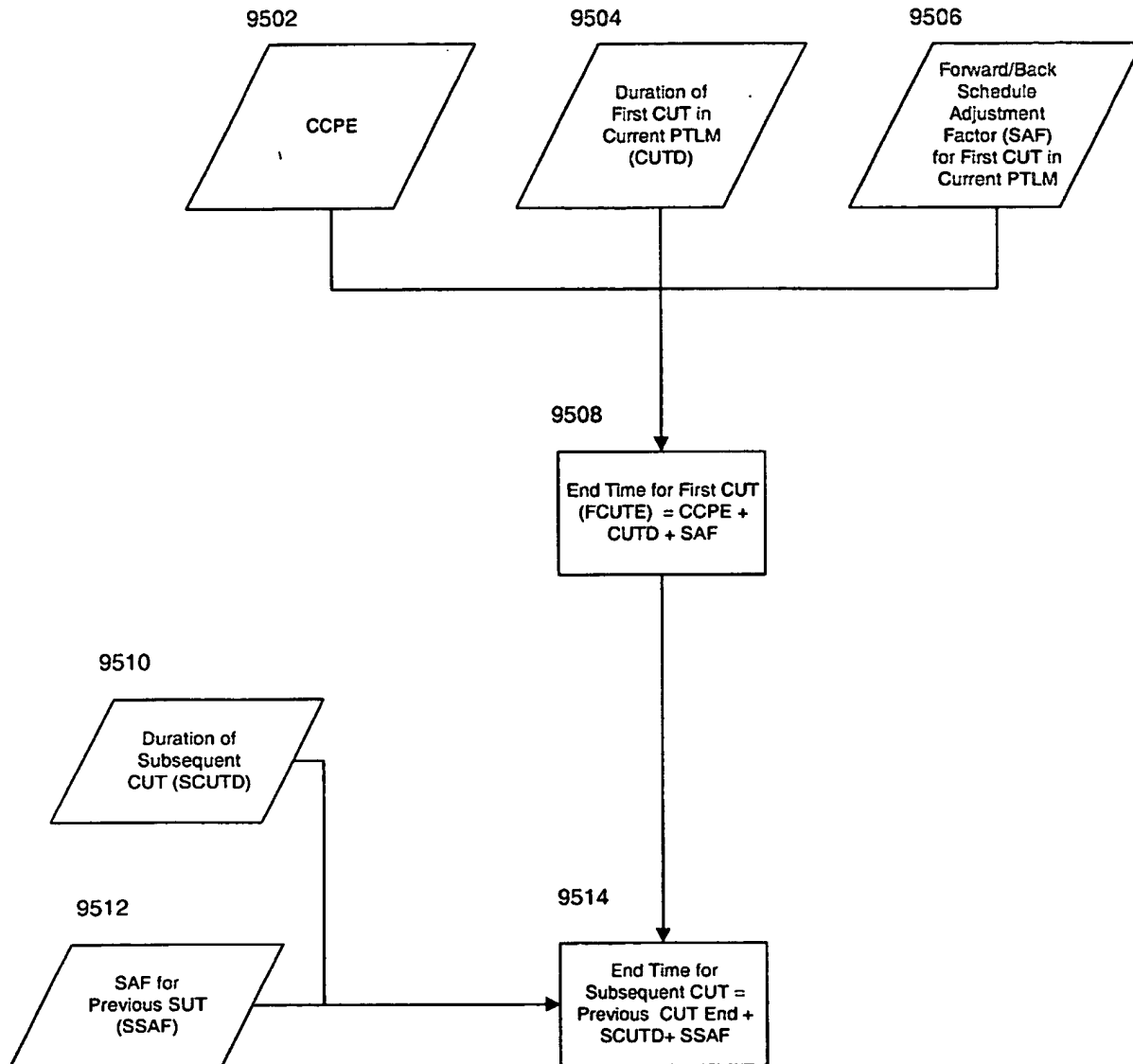


FIG. 95



Master Process Parameter Table - Biopharmaceutical

Unit Operation Type	Group 1			Group 2			Group 3		
	Parameter	Set	Units	Parameter	Set	Units	Parameter	Set	Units
11 Necrosis Prep	Number of flasks Media Volume/flask		2 0.25 Ltr	Temperature Agitation Duration		37 C 200 RPM 10 Hours	Final OD		12
12 Post Growth	Scale Up Ratio Media Volume/flask		10 Fold 1.25 L	Temperature Agitation Duration		37 C 200 RPM 10 Hours	Final OD		12
13 Fermentation Production	Scale Up Ratio Fermenter Working Volume Antibiotic A Antibiotic B Base Add	S-101 S-102 S-103 S-104 S-105	10 Fold 500 Ltr 1 M/L 1 M/L 5 M/L 5 M/L	Growth Temperature Agitation Stirrer Rate Reactor Pressure Total Duration		37 C 200 RPM 1.5 W/L 2 PSID 21 Hrs	Final OD Dry Cell Mass Product Concentration CIP	12 Y	9.90 Gm TDC/A 0.3 Gm Product
14 Cell Washing	Number of Ampoules Volume Per Ampoule Starting Cell Density Ampoule Split Ratio Culture Vessel Type Feed Volume		2 MB 300,000 Cells/Amp 1 Vessel/Ampoule Rat. Rat. 100:1	Serum Control Feed Rate Days to Confluence		2.0% Feed Bovine Serum 1 Feed per vessel per 2 Days 2 Days	Amplification Factor		100%
15 Culture Vessel Split	Vessel Split Ratio Feed Vessel Type Feed Volume Serum Content		2 100 ml 2.0% Feed Bovine Serum	Feed Rate Days to Confluence		1 Feed per vessel per 2 Days 2 Days	Amplification Factor		100%
16 Spore/Film Banking	Flask Feed Volume Vessel/Film Ratio Ampoule Density Number of PBS Washes Number of Media Washes No. of Media/Serum Washes		4 Ltr 0.1 L Cell/A, Flak 5 G/Ltr 2 1 2	Serum Control Feed Rate Days to Confluence		2.0% Feed Bovine Serum 1 Feed per vessel per 2 Days 2 Days	Amplification Factor		100%
17 Bioreactor Preparation (2nd Tank Reactor)	Reactor Feed Volume Spore/Film Ratio Ampoule Density Number of PBS Washes Number of Media Washes No. of Media/Serum Washes		400 Ltr 80 5 G/Ltr 2 1 2	Serum Control Feed Rate Days to Confluence Serum/Film Match Washes		2.0% Feed Bovine Serum 1 Feed per vessel per 2 Days 2 Days	Product Concentration Total Protein Content		2400% Mg Protein 0.175 Mg Protein
18 Bioreactor Preparation (Medium Flow Reactor)	Reactor Feed Volume Number of PBS Washes Number of Media Washes No. of Media/Serum Washes Serum Content		100 Ltr 2 2 2 2.0% Feed Bovine Serum	Number of Reaction Feed Rate Days to Confluence		1 Feed per vessel per 1 Days 10 Days	Harvest Volume Product Concentration Total Protein Content		100% Ltr 25 Mg Protein 0.125 Mg Protein
19 Bioreactor Preparation (Packaged Reactor)	Reactor Feed Volume Ampoule Density Number of PBS Washes Number of Media Washes No. of Media/Serum Washes Serum Content		1 Ltr Gm/A 2 2 2	Number of Reaction Feed Rate Days to Confluence		1 Feed per vessel per 1 Days 10 Days	Product Concentration Total Protein Content		2500% Mg Protein 0.125 Mg Protein
113 Product Testing	Number of Ampoules Volume Per Ampoule Starting Cell Density Ampoule Split Ratio		2 300,000 Cells/Amp 1 Vessel/Ampoule	Serum Control Feed Rate Days to Confluence		2.0% Feed Bovine Serum 1 Feed per vessel per 2 Days 2 Days	Amplification Factor		100%

FIG 96A

Water Encaps Parameters Table • Biopharmaceutical

[illegible]

FIG. 96B

Master Process Parameters Table - Biopharmaceutical

Unit Operation Type	Group 1		Group 2		Group 3	
	Parameter	Units	Parameter	Units	Parameter	Units
121 Product P1 by Soln						
	Reagent Concentration	1 M	Reagent/Unit Product Temperature Addition Time Additional Mix Time	0.25 Kg/L 4 C 0.5 Hours 2 Hours	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SIP	95% 95% Y Y Y
122 Product P1 by Liquor						
	Reagent Concentration	1 M	Reagent/Unit Product Temperature Addition Time Additional Mix Time	0.25 Kg/L 4 C 0.5 Hours 2 Hours	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SIP	95% 95% Y Y Y
123 Concentrant P1 by Soln						
	Reagent Concentration	1 M	Reagent/Unit Product Temperature Addition Time Additional Mix Time	0.25 Kg/L 4 C 0.5 Hours 2 Hours	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SIP	95% 95% Y Y Y
124 Concentrant P1 by Liquor						
	Reagent Concentration	1 M	Reagent/Unit Product Temperature Addition Time Additional Mix Time	0.25 Kg/L 4 C 0.5 Hours 2 Hours	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SIP	95% 95% Y Y Y
125 Solids Harvest Targeted Flow MP						
	Reagent Concentration	0.3 M 11 L/SF/HR at 40 Ppt at 4 C 400 L/SF/HR	Reagent/Unit Product Temperature Addition Time Additional Mix Time	0.25 Kg/L 4 C 0.5 Hours 2 Hours	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SIP	95% 95% Y Y Y
126 Concentration Harvest						
	Reagent Concentration	0.3 M 11 L/SF/HR at 40 Ppt at 4 C 400 L/SF/HR	Reagent/Unit Product Temperature Addition Time Additional Mix Time	0.25 Kg/L 4 C 0.5 Hours 2 Hours	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SIP	95% 95% Y Y Y
127 Concentration Harvest						
	Reagent Concentration	0.3 M 11 L/SF/HR at 40 Ppt at 4 C 400 L/SF/HR	Reagent/Unit Product Temperature Addition Time Additional Mix Time	0.25 Kg/L 4 C 0.5 Hours 2 Hours	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SIP	95% 95% Y Y Y
128 Concentration Harvest						
	Reagent Concentration	0.3 M 11 L/SF/HR at 40 Ppt at 4 C 400 L/SF/HR	Reagent/Unit Product Temperature Addition Time Additional Mix Time	0.25 Kg/L 4 C 0.5 Hours 2 Hours	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SIP	95% 95% Y Y Y
129 Concentration Harvest						
	Reagent Concentration	0.3 M 11 L/SF/HR at 40 Ppt at 4 C 400 L/SF/HR	Reagent/Unit Product Temperature Addition Time Additional Mix Time	0.25 Kg/L 4 C 0.5 Hours 2 Hours	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SIP	95% 95% Y Y Y

FIG. 96C

Unit Operation Type	Group 1			Group 2			Group 3		
	Parameter	Set	Set	Parameter	Set	Set	Parameter	Set	Set
	Column Aspect Ratio Max. Linear Velocity		0.37 MD 100 Cnfrs at 43 Pdg and 4 C	Column Eff A Column Eff B Column Regime Column Store		3 Column Volumes 0 Column Volumes 1 Column Volumes 2 Column Volumes	Step Recovery of T.P. Temperature Regulation CIP	N Y Y	95%
T140 Prod. Act. Chromatography HPLC	Column Capacity Column Overload Factor Column Aspect Ratio Max. Linear Velocity		10 MD Prod. Act. of Peptide 1.3 Fold 0.37 MD 100 Cnfrs at 43 Pdg and 4 C	Column Equilibration Column Wash Column Eff A Column Eff B Column Regime Column Store		5 Column Volumes 3 Column Volumes 3 Column Volumes 2 Column Volumes 1 Column Volumes 2 Column Volumes	Prod. Elution Volume Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	N Y Y Y Y	42% 95% 95%
T141 Cont. Act. Chromatography HPLC	Column Capacity Column Overload Factor Column Aspect Ratio Max. Linear Velocity		10 MD Cont. Act. of Peptide 1.3 Fold 0.37 MD 100 Cnfrs at 43 Pdg and 4 C	Column Equilibration Column Wash Column Eff A Column Eff B Column Regime Column Store		5 Column Volumes 3 Column Volumes 3 Column Volumes 2 Column Volumes 1 Column Volumes 2 Column Volumes	Prod. Elution Volume Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	N Y Y Y Y	42% 95% 95%
T142 Cont. Act. Chromatography HPLC	Column Capacity Column Overload Factor Column Aspect Ratio Max. Linear Velocity		10 MD Cont. Act. of Peptide 1.3 Fold 0.37 MD 100 Cnfrs at 43 Pdg and 4 C	Column Equilibration Column Wash Column Eff A Column Eff B Column Regime Column Store		5 Column Volumes 3 Column Volumes 3 Column Volumes 2 Column Volumes 1 Column Volumes 2 Column Volumes	Prod. Elution Volume Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	N Y Y Y Y	42% 95% 95%
T143 Cont. Act. Chromatography HPLC	Column Capacity Column Overload Factor Column Aspect Ratio Max. Linear Velocity		10 MD Cont. Act. of Peptide 1.3 Fold 0.37 MD 100 Cnfrs at 43 Pdg and 4 C	Column Equilibration Column Wash Column Eff A Column Eff B Column Regime Column Store		5 Column Volumes 3 Column Volumes 3 Column Volumes 2 Column Volumes 1 Column Volumes 2 Column Volumes	Prod. Elution Volume Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	N Y Y Y Y	42% 95% 95%
T144 Size Excl. Chromatography HPLC	Load Capacity Length Max. Linear Velocity Void Volume		3% of Total Column Volume 100 Cnfrs at 100 Cnfrs at 43 Pdg and 4 C 25% Column Volume	Column Equilibration Column Wash Column Regime Column Store		4 Column Volumes 1 Column Volumes 1 Column Volumes 2 Column Volumes	Prod. Elution Volume Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	N Y Y Y Y	42% 95% 95%
T145 Size Excl. Chromatography HPLC	Load Capacity Length Max. Linear Velocity Void Volume		3% of Total Column Volume 100 Cnfrs at 100 Cnfrs at 43 Pdg and 4 C 25% Column Volume	Column Equilibration Column Wash Column Regime Column Store		4 Column Volumes 1 Column Volumes 1 Column Volumes 2 Column Volumes	Prod. Elution Volume Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	N Y Y Y Y	42% 95% 95%
T146 Size Excl. Chromatography HPLC	Load Capacity Length Max. Linear Velocity Void Volume		3% of Total Column Volume 100 Cnfrs at 100 Cnfrs at 43 Pdg and 4 C 25% Column Volume	Column Equilibration Column Wash Column Regime Column Store		4 Column Volumes 1 Column Volumes 1 Column Volumes 2 Column Volumes	Prod. Elution Volume Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	N Y Y Y Y	42% 95% 95%
T147 Elution	Elution Factor		3 Liter/Unit	Elution Time Additional Mix Time		0.5 Hour 1 Hour	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	N Y Y Y Y	95% 95%
T148 Revalidation	Reagent/Product Ratio Dissolution Time Additional Mix Time		0 L/kg Product 0.50 Hour 0.10 Hour	Reagent 1 Concentration		Water Dist.	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	N Y Y Y Y	95% 95%

File. 90E

Master Process Parameters Table - Biopharmaceutical

Unit Operation Type	Group 1			Group 2			Group 3		
	Parameter	Units	Set	Parameter	Units	Set	Parameter	Units	Set
T10 Enzymatic Hydrolysis	Enzyme to Product Ratio	0.04 U/ml of Enzyme Stock Per Utr of Sub. Proc. Vol		Hydrolysis Solution 1			Stop Recovery of Product		95%
	Enzyme Concentration	2 mg/ml		Hydrolysis Solution 2			Stop Recovery of T.P.		95%
	Reaction Temp.	37 Degrees C		Hydrolysis			Temperature Regulation		Y
	Reaction Duration	30 Minutes					CIP		Y
T110 Application	Product Capacity/Load	8 Units		Application Time			Stop Recovery of Product		95%
	Product Unit Size	100 Grams/Unit		Product Weight Reduction			Stop Recovery of T.P.		95%
T111 Heat Exchange	Process Initial Temp	81.5 Degrees C		Exposure Time			CIP		Y
	Process Final Temp	39.2 Degrees C					CIP		Y
	Utility Initial Temp	34 Degrees C					Stop Recovery of Product		100%
	Utility Final Temp	8 Degrees C					Stop Recovery of T.P.		100%
T112 Storage	Process Operating Pressure	23.5 K BTU/Hr					Temperature Regulation		Y
	Design Type (T/C)	P					CIP		Y
T113 Fermentation	Scale Up Ratio	10 Fold		Growth Temperature			Stop Recovery of Product		95%
	Fermenter Working Volume	50 Liters		Aeration			Stop Recovery of T.P.		95%
	Antibiotic A	1 M/L		Sparging Rate			Temperature Regulation		Y
	Antibiotic B	1 M/L		Recirculation			CIP		Y
S4 Final Seeding	Final Seed Volume	12 Liters		Seeding Concentration			Stop Recovery of Product		95%
	Spore Density	4 G/L		Feed Rate			Stop Recovery of T.P.		95%
	Number of PBS Washes	5 G/L		Oxygen Concentration			Temperature Regulation		Y
	Number of Media Washes	2 PBS					CIP		Y
S5 Culture Vial Sp. 1	Final Seed Volume	12 Liters		Seeding Concentration			Stop Recovery of Product		95%
	Spore Density	4 G/L		Feed Rate			Stop Recovery of T.P.		95%
	Number of PBS Washes	5 G/L		Oxygen Concentration			Temperature Regulation		Y
	Number of Media Washes	2 PBS					CIP		Y
S6 Culture Vial Sp. 2	Final Seed Volume	12 Liters		Seeding Concentration			Stop Recovery of Product		95%
	Spore Density	4 G/L		Feed Rate			Stop Recovery of T.P.		95%
	Number of PBS Washes	5 G/L		Oxygen Concentration			Temperature Regulation		Y
	Number of Media Washes	2 PBS					CIP		Y
S7 Culture Vial Sp. 3	Final Seed Volume	12 Liters		Seeding Concentration			Stop Recovery of Product		95%
	Spore Density	4 G/L		Feed Rate			Stop Recovery of T.P.		95%
	Number of PBS Washes	5 G/L		Oxygen Concentration			Temperature Regulation		Y
	Number of Media Washes	2 PBS					CIP		Y
S8 Filled Batch Reactor	Process Initial Temp	37 Degrees C		Exposure Time			Stop Recovery of Product		95%
	Process Final Temp	4 Degrees C					Stop Recovery of T.P.		95%
	Utility Initial Temp	3 Degrees C					Temperature Regulation		Y
	Utility Final Temp	2 Degrees C					CIP		Y

FIG. 96F

Master Process Parameters Table - Biopharmaceutical

Unit Operation Type	Group 1		Group 2		Group 3	
	Parameter	Setp.	Parameter	Setp.	Parameter	Setp.
	Utility Feed Temp. Process Specific Heat On sign Type (P, T, C)	5 Degrees C 12 K BTU/hr P			Temperature Regulation CIP SIP	Y Y Y
57 Liquid/Liquid Extraction	Liquid/Liquid Ratio Extraction Temperature Acidulation Duration Additional Mix Duration Mix Energy	1 L Extractant/ Product 4 C 0.5 Hours 4 Hours 0.3 HPT/100 L	Phase Separation Time Product Phase (Top/Bottom) Harvest Time	1000% Hours Top 0.5 Hours	Strip Recovery of Product Strip Recovery of T.P. Temperature Regulation CIP SIP	Y Y Y Y Y
60 Sol. Solvent Extraction	Liquid/Liquid Ratio Extraction Temperature Duration Mix Energy	1 L Extractant/ Product 4 C 4 Hours 0.3 HPT/100 L	Phase Separation Time Product Phase (Top/Bottom) Harvest Time	1000% Hours Top 0.5 Hours	Strip Recovery of Product Strip Recovery of T.P. Temperature Regulation CIP SIP	Y Y Y Y Y

FIG. 94 G

INTERNATIONAL SEARCH REPORT

International application
PCT/US00/22104No. **A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : G06G 7/48, 7/58

US CL : 703/6, 12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 703/6, 12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

IEEE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,237,508 A (FURUKAWA et al.) 17 August 1993, fig. 3-5, 20-23, 41 60-63.	1-3
X	KETCHAM et al. A Generic Simulator for Continuous Flow Manufacturing; IEEE 1988 Winter Simulation Conf. Proc. pages 610-613.	1-3
X	LIT, J. An Expert System to Perform On-line Tuning IEEE Control Systems Magazine; April 1991. Vol. 11. No. 3. pages 19-22.	1-3

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Date of the actual completion of the international search

27 DECEMBER 2000

Date of mailing of the international search report

25 JAN 2001

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